PB91-143388

Drinking Water Criteria Document for 1,2-Dichloropropane

Syracuse Research Corp., NY

Prepared for:

Environmental Protection Agency, Cincinnati, OH

3 Aug 90

U.S. Department of Commerce
National Technical Information Service
NTIS

PB89-192322/AS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before comple

1. REPORT NO.	2.	3 PB91-143388
ECAO-CINN-404		

4. TITLE AND SUBTITLE	5. REPORT DATE
Drinking Water Criteria Document for 1,2-Dichloro-propane	Aug. 1990
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO
Environmental Criteria and Assessment Office	ECAO-CINN-404
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
Environmental Criteria and Assessment Office OHEA/USEPA Cinn., OH	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Office of Drinking Water Criteria and Standards Division Washington, DC 20460	14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

This document is to supersede old document PB89-193222/AS

16. ABSTRACT

This document deals with the drinking water health effects of 1,2-Dichloropropane through the review of several studies. These studies include animal and humans. Physical and chemical properties are discussed. Carcinogenicity of the compound is reviewed and evaluated through various studies. Any existing guidelines and standards are presented.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field. Group
health effects, drinking water, animal studies, cancer risk, cancerous, criteria standards, criteria document, human studies, 1,2-Dichloropropane		

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
	20. SECURITY CLASS (This page)	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

NTIS

EPA

United States
Environmental Protection
Agency

Revised 6/13/90
8/3/90

FINAL
ECAO-CIN-404
~~April 1, 1987~~

Research and Development

PB91-143388

DRINKING WATER CRITERIA DOCUMENT FOR 1,2-DICHLOROPROPANE

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1986; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

Michael B. Cook
Director
Office of Drinking Water

DOCUMENT DEVELOPMENT

David J. Reisman, Document Manager
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Helen H. Ball, Project Officer
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Authors

Dipak K. Basu
J. Robotti Anderson
Joan T. Coleman
Syracuse Research Corporation
Syracuse, New York
(Contract 68-03-3112)

Revised Chapter 8

David J. Reisman
Charles Hiremath
Charles Ris
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency

Scientific Reviewers

James W. Holder
Bernard Haberman
Carcinogen Assessment Group
U.S. Environmental Protection Agency
Washington, DC

Yogendra Patel
Jennifer Orme
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC

Document Preparation

Technical Support Services Staff: C. Cooper, P. Daunt, C. Fessler, K. Mann, B. Zwayer, Environmental Criteria and Assessment Office, Cincinnati

W. Bruce Peirano
C. Sonich-Mullin
Michael L. Dourson
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Editorial Reviewers

Erma Durden
Judith Olsen
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

TABLE OF CONTENTS

		Page
I.	SUMMARY	I-1
II.	PHYSICAL AND CHEMICAL PROPERTIES	II-1
	INFORMATION AND PROPERTIES	II-1
	FATE OF 1,2-DICHLOROPROPANE IN WATER	II-1
	SUMMARY	II-3
III.	TOXICOKINETICS	III-1
	HUMAN DATA	III-1
	ANIMAL DATA	III-1
	Absorption	III-1
	Distribution and Retention	III-1
	Metabolism	III-2
	Excretion	III-3
	SUMMARY	III-5
IV.	HUMAN EXPOSURE (to be provided by Office of Drinking Water)	IV-1
V.	HEALTH EFFECTS IN ANIMALS	V-1
	ACUTE AND SHORT-TERM TOXICITY	V-1
	Subchronic Toxicity	V-17
	Chronic Toxicity	V-21
	TARGET ORGAN TOXICITY	V-23
	OTHER EFFECTS	V-25
	Carcinogenicity	V-25
	Mutagenicity	V-33
	Teratogenicity and Other Reproductive Effects	V-36
	SUMMARY	V-36
VI.	HEALTH EFFECTS IN HUMANS	VI-1
	SUMMARY	VI-1
VII.	MECHANISMS OF TOXICITY	VII-1
	SUMMARY	VII-1

TABLE OF CONTENTS (cont.)

		Page
VIII.	QUANTIFICATION OF TOXICOLOGICAL EFFECTS	VIII-1
	INTRODUCTION	VIII-1
	NONCARCINOGENIC EFFECTS	VIII-6
	QUANTIFICATION OF NONCARCINOGENIC EFFECTS	VIII-11
	Derivation of 1-Day HA	VIII-11
	Derivation of 10-Day HA	VIII-12
	Derivation of Longer-term HA	VIII-14
	Assessment of Lifetime Exposure and Derivation of a DWEL	VIII-14
	CARCINOGENIC EFFECTS	VIII-15
	QUANTIFICATION OF CARCINOGENIC EFFECTS	VIII-16
	EXISTING GUIDELINES AND STANDARDS	VIII-18
	SPECIAL CONSIDERATIONS	VIII-19
	Synergistic Effects	VIII-19
	High Risk Subpopulations	VIII-20
	SUMMARY	VIII-20
IX.	REFERENCES	IX-1

LIST OF TABLES

No.	Title	Page
II-1	Physical and Chemical Properties of 1,2-Dichloropropane . .	II-2
IV-1	Estimated Respiratory Intake of 1,2-Dichloropropane	IV-4
IV-2	Estimated Intake of 1,2-Dichloropropane from the Environment by Adult Males in µg/kg/day	IV-6
V-1	Acute and Short-term Toxic Effects of 1,2-Dichloropropane .	V-2
V-2	Effects of Subchronic Exposure of Experimental Animals to 1,2-Dichloropropane.	V-12
V-3	Summary of Gavage Carcinogenesis Bioassay of 1,2-Dichloropropane	V-26
V-4	Mutagenicity/Clastogenicity of 1,2-Dichloropropane.	V-34
VIII-1	Data Used for the Derivation of q_1^*	VIII-17
VIII-2	Criteria for 1,2-Dichloropropane.	VIII-21

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ATPase	Adenosine triphosphatase
bw	Body weight
CNS	Central nervous system
DWEL	Drinking water equivalent level
GI	Gastrointestinal
HA	Health advisory
LD_{50}	Dose lethal to 50% of the recipients
LOAEL	Lowest-observed-adverse-effect level
MTD	Maximum tolerated dose
NADP	Nicotinamide-adenine dinucleotide phosphate
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OCT	Ornithine carbamyl transferase
ppm	Parts per million
SCE	Sister-chromatid exchange
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
V/V	Volume per volume

I. SUMMARY

1,2-Dichloropropane is a colorless liquid used as an insecticidal fumigant, chemical intermediate, solvent, scouring compound, spotting agent and a metal degreasing compound. It has a molecular weight of 113.0, specific gravity of 1.1593 (20/20°C), a vapor pressure of 50 mm Hg at 25°C, a boiling point of 96.6°C, a freezing point of -100.44°C and a water solubility of 2.7 g/ℓ at 20°C. This compound may undergo significant biodegradation during normal wastewater treatment but is resistant to degradation in natural surface waters. Evaporation may be the primary mode of loss of this compound from aquatic media.

Pertinent data regarding the toxicokinetic profile of 1,2-dichloropropane in humans were not located in the available literature. Data on experimental animals, however, suggest that this compound is almost completely absorbed (95%) and rapidly excreted from the tissues of rats following oral administration. The metabolic pathway for 1,2-dichloropropane involves the formation of N-acetyl-S-(2-hydroxy propyl) cysteine, the major urinary metabolite, and N-acetyl-S-(2,3-dihydroxy propyl) cysteine. The major route of elimination in mammals is by urinary excretion.

The acute oral LD_{50} for 1,2-dichloropropane reported in the literature range from ~860-5000 mg/kg for mice and dogs, respectively, with other species being intermediate in sensitivity. A dosage of 2000 mg/kg/day by gavage for 14 days was lethal to mice and rats; deaths occurred among mice but not rats at 500 or 1000 mg/kg/day. Some evidence for renal effects (redness of the renal medullae) was seen at doses of 125-2000 mg/kg/day in

mice and at 2000 mg/kg/day in rats. A number of studies evaluating the effects of acute vapor exposure to 1,2-dichloropropane reported kidney, liver and adrenal degeneration in rats and guinea pigs that received 10,400 mg/m^3 (~2200 ppm) for one or a few 7-hour exposures.

Subchronic, oral exposure of rats and mice to 1,2-dichloropropane resulted in liver congestion, hepatic fatty changes and liver necrosis in rats receiving 1000 mg/kg/day, 5 days/week for 13 weeks. Slightly depressed body weight was reported in mice treated with 500 mg/kg/day on 5 days/week for 13 weeks. Subchronic studies involving inhalation of 1,2-dichloropropane reported slight liver degeneration, renal and adrenal effects, reduced growth rates, CNS abnormalities and disruption of enzyme activities.

The effects of chronic oral exposure to 1,2-dichloropropane in rats included decreased survival, hepatic foci of clear cell change and hepatic necrosis in females treated with 250 mg/kg/day (5 days/week) and mammary gland hyperplasia in females treated with 125 mg/kg/day (5 days/week). Males that received 62 mg/kg/day (5 days/week) showed no effects. In mice given 125 or 250 mg/kg/day (5 days/week), decreased survival occurred in females, liver lesions (hepatocytomegaly and hepatic necrosis) were observed in males, and slight acanthosis of the forestomach epithelium was found in both males and females.

The principal target organ for 1,2-dichloropropane toxicity appears to be the liver. Non-neoplastic lesions identified as centrilobular necrosis have been reported in animals and in one human. Effects on the kidney, adrenal and lung have also been reported in animal studies.

1,2-Dichloropropane elicited positive responses in reverse mutation assays with Salmonella typhimurium and in forward mutation assays with Aspergillus nidulans. It was also active in in vitro sister-chromatid exchange and chromosome aberration assays with hamster ovary cells.

When administered orally, 1,2-dichloropropane produced statistically significant increases in the incidence of liver adenomas and carcinomas in both male and female B6C3F1 mice. Carcinomas alone were also elevated. There was marginal evidence of carcinogenicity in female rats, as indicated by a trend incidence of adenocarcinomas in the mammary gland. Consideration of the direct bioassay evidence leads to a Group C weight of evidence classification according to the U.S. EPA (1986b) guidelines. However, because of the evidence of mutagenic activity, the knowledge that intermediate metabolites include two suspect carcinogens, and the structural similarity with three other compounds found to be carcinogenic in animal test systems, the U.S. EPA Carcinogen Assessment Group classified this chemical in Group B2. According to the U.S. EPA (1986b) Guidelines for Carcinogen Risk Assessment, Group B2 chemicals include "agents for which there is sufficient evidence from animal studies and for which there is inadequate evidence or no data from epidemiologic studies."

1,2-Dichloropropane and trichloropropane did not act synergistically with respect to liver damage in rats, as evidenced by levels of serum enzymes. Human data that would establish the existence of subpopulations having a special sensitivity to 1,2-dichloropropane were not available. Animal data suggest considerable inter- and intraspecies differences in sensitivity to this compound, and that younger individuals may be more

sensitive to 1,2-dichloropropane than adults. Agricultural and industrial workers who are occupationally exposed to 1,2-dichloropropane may be at somewhat greater risk because of their additional exposure.

The data base for the toxicity of 1,2-dichloropropane is limited to a number of studies from the older literature and an NTP toxicology and carcinogenicity study. Thus, because of the inadequacy of the available toxicological studies, 1-day, 10-day and longer-term HAs are not recommended. A lifetime DWEL is not recommended because of the carcinoginic potency of 1,2-dichloropropane.

Because there is evidence that 1,2-dichloropropane may be carcinogenic to humans, the dose-response data for hepatocellular adenoma and carcinoma in male mice (NTP, 1986) were used to estimate (using a linearized multi-stage model) the concentrations of 1,2-dichloropropane in drinking water that would result in increased lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6}. The corresponding water concentrations are 5.2×10^{-2}, 5.2×10^{-3} and 5.2×10^{-4} mg/L, respectively. These risk estimates are slightly lower than those given in the earlier (1985) draft of this document because of the change in incidence data from the NTP (1983) draft and the NTP (1986) final publication.

II. PHYSICAL AND CHEMICAL PROPERTIES

Information and Properties

1,2-Dichloropropane is also known as propylene dichloride (BCPC, 1977). It is a colorless, stable liquid used as an insecticidal fumigant and is prepared by the chlorination of propylene. Generally, it is used as a mixture with other fumigants; the technical formulation "Dowfume EB-5" (Dow Chemical Company) is composed of 7.2% ethylene dichloride, 29.5% 1,2-dichloropropane and 63.6% carbon tetrachloride (BCPC, 1977). 1,2-Dichloropropane is also used as a chemical intermediate, lead scavenger for antiknock fluids, solvent, scouring compound, spotting agent and a metal degreasing agent (Hawley, 1977).

Structure: $ClCH_2CHClCH_3$

Molecular formula: $C_3H_6Cl_2$

Molecular weight: 113.0

Chemical Abstract Service (CAS) registry number: 78-87-5

Registry of Toxic Effects of Chemical Substances (RTECS) number: TX9625000

1,2-Dichloropropane also has a chloroform-like odor (Hawley, 1977). The chemical and physical properties of 1,2-dichloropropane are listed in Table II-1.

Fate of 1,2-Dichloropropane in Water

1,2-Dichloropropane is relatively stable in water; it will not photolyze, since there are no chromophores to absorb light at wavelengths common to the troposphere (Callahan et al., 1979). It will not biodegrade significantly in surface waters (Kawasaki, 1980), although some biodegradation may take place in sewage treatment plants (Tabak et al., 1981). It will not

TABLE II-1

Physical and Chemical Properties
of 1,2-Dichloropropane*

Property	Value
Specific gravity	1.1593 (20/20°C)
Freezing point	-100.44°C
Boiling point	96.6°C
Vapor pressure	50 mm Hg at 25°C
Refractive index	1.437 at 25°C
Solubility	2700 mg/ℓ water at 20°C; soluble in alcohol, ethyl ether
Flash point (BCPC, 1977)	21°C
Ignition Temperature	557-570°C

*Source: Torkelson and Rowe (1981).

Conversion: 1 mg/m^3 = 0.217 ppm and 1 ppm = 4.62 mg/m^3 at 25°C, 760 mm Hg

sorb significantly to biota or sediments, based on the octanol/water partition coefficient of 100 (Hansch and Leo, 1979). Some hydrolysis will occur at ambient temperatures; the hydrolysis half-life based on a hydrolysis rate constant of 7.2×10^{-4} hour^{-1} (25°C) is ~40 days (Mabey et al., 1981). In open waters, the dominant removal process is volatilization. An EXAMS model of the fate of 1,2-dichloropropane in a pond, river and two lakes yielded volatilization half-lives of 1.7-10 days (Burns et al., 1981). 1,2-Dichloropropane has been detected in the aqueous environment in industrial areas (Ohio River Valley Water Sanit. Comm., 1979, 1980; Dewalle and Chian, 1978; Dreisch et al., 1980).

Summary

1,2-Dichloropropane is a colorless, stable liquid used as an insecticidal fumigant; chemical intermediate, solvent, scouring compound, spotting agent and a metal degreasing compound (Hawley, 1977). It has a molecular weight of 113.0, vapor pressure of 50 mm Hg at 25°C, and a solubility of 2700 mg/L water at 20°C (BCPC, 1977). This compound may undergo significant biodegradation during normal wastewater treatment with activated sludge but is resistant towards biodegradation in natural surface waters. It appears that evaporation may be the primary mode of loss of this compound from aquatic media (Chiou et al., 1980; Kawasaki 1980, Tabak et al., 1981).

III. TOXICOKINETICS

Human Data

Data regarding the absorption, distribution, metabolism or excretion of 1,2-dichloropropane in humans were not located in the available literature.

Animal Data

Absorption. Information on the absorption of 1,2-dichloropropane was not located in the available literature; however, some inferences can be made from the distribution and excretion study of Hutson et al. (1971). 1,2-Dichloro[1-^{14}C]propane (0.88 mg/rat; ~4 mg/kg) in 0.5 mL arachis oil was administered by gavage to adult male and female rats. Excretion of radioactivity in the urine and feces was monitored. The excretion of radioactivity in expired air was studied following similar administration of a slightly higher dose (1.07 mg/rat; ~4.8 mg/kg) to female rats. Within 96 hours, ~95% of the administered radioactivity was excreted in the urine and expired air of female rats. Absorption of the compound from the gastrointestinal tract appears to be relatively complete since only ~5% of the radioactivity was recovered from the feces. Fecal recovery may have been from biliary excretion or unabsorbed compound but was not determined in this study (Hutson et al., 1971). Male rats appeared to respond similarly but exhalation excretion data were not reported, disallowing a quantitative estimation of absorption.

Distribution and Retention. Hutson et al. (1971) studied the excretion and retention of 1,2-dichloro[1-^{14}C]propane in 6 male and 6 female rats. Each animal was administered a single dose of 0.88 mg 1,2-dichloro-[1-^{14}C]propane (~4 mg/kg) in 0.5 mL arachis oil and sacrificed after

4 days. Approximately 0.5% of the administered radioactivity was recovered from the gut of the animals within 96 hours, 1.6% was recovered from the skin and 3.6% was detected in the carcass. The total residual radioactivity recovered in these tissues in both male and female animals 4 days following administration was ~5.7%. The total radioactivity recovered within 96 hours in the tissues, urine, feces and expired air (see Excretion Section) of female rats accounted for 106.8% of the dose. Data for male rats were similar but measurements of radioactivity in expired air were not conducted and a total recovery value was not presented. The authors stated that 80-90% of the radioactivity was excreted within 24 hours, although data for tissue levels and expired air were not provided for this time period.

Metabolism. The metabolism of 1,2-dichloropropane has been studied in vitro by Van Dyke and Wineman (1971) using supernatant and microsomes from male rat liver. [^{36}Cl]-1,2-dichloropropane was incubated with microsomes, NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase and the 105,000 x g supernatant fraction. In this metabolism system, 1,2-dichloropropane was enzymatically dechlorinated so that ~5.8% of the available chlorine was removed from the organic moiety within 30 minutes. Jones and Gibson (1980) further characterized the metabolism of 1,2-dichloropropane using rat liver microsomes. 1,2-Dichloropropane (10 μM) was incubated with 15,000 x g supernatant from rat liver and reduced glutathione (500 μM). After 2 hours, the thiol content of the medium was not reduced, thus, no glutathione conjugates had formed. In the same study, Sprague-Dawley rats were gavaged 20 mg/kg 1,2-dichloropropane as a solution in propane-1,2-diol each day for 4 days. N-acetyl-S-(2-hydroxypropyl) cysteine was isolated as a major urinary metabolite. The authors revealed that at

least 25-35% of a single dose of 1,2-dichloropropane was excreted as this conjugate. The proposed pathways of 1,2-dichloropropane metabolism are summarized in Figure III-1. According to the authors, 1,2-dichloropropane was dechlorinated, oxidized, and conjugated to ultimately yield N-acetyl-S-(2-hydroxypropyl) cysteine. 1,2-Epoxypropane, derived from 1-chloro-2-hydroxypropane was a proposed metabolite. This epoxide was hydrolyzed in the rat to propane-1,2-diol, a nontoxic compound that is further metabolized to lactate and CO_2. B-Chlorolactate was identified as a minor metabolite of 1,2-dichloropropane. This compound was derived from 1-chloro-2-hydroxypropane and further oxidized to oxalate. Finally, it was established that 3-chloropropane-1,2-diol was metabolized to N-acetyl-S-(2,3-dihydroxypropyl) cysteine, probably by 2,3-epoxypropane-1-ol (Jones and Gibson, 1980).

Excretion. Twenty-four hours following the administration of 0.88 mg 1,2-dichloro[1-^{14}C]propane/rat (~4 mg/kg) by gavage in 0.5 mL arachis oil to male and female rats, ~50% of the radioactivity was excreted in the urine and 4.4% was excreted in the feces. Within 96 hours, the total amount of radioactivity recovered from the urine of animals of both sexes was ~53% of that administered. Fecal elimination accounted for ~6% of the administered radioactive dose (Hutson et al., 1971). In a second experiment, five female rats were dosed orally with 1.07 mg 1,2-dichloro-[1-^{14}C]propane/rat (~4.8 mg/rat). Within 96 hours of dosing, ~19.3% of the administered radioactivity was recovered in the expired air as [^{14}C] carbon dioxide and 23.1% was recovered as other volatile radioactivity (Hutson et al., 1971). The authors stated that a portion of the administered 1,2-dichloropropane may have been exhaled as 1,2-dichloropropane through the lungs of the rats; however, the compound did undergo metabolism as indicated by the 19.3%

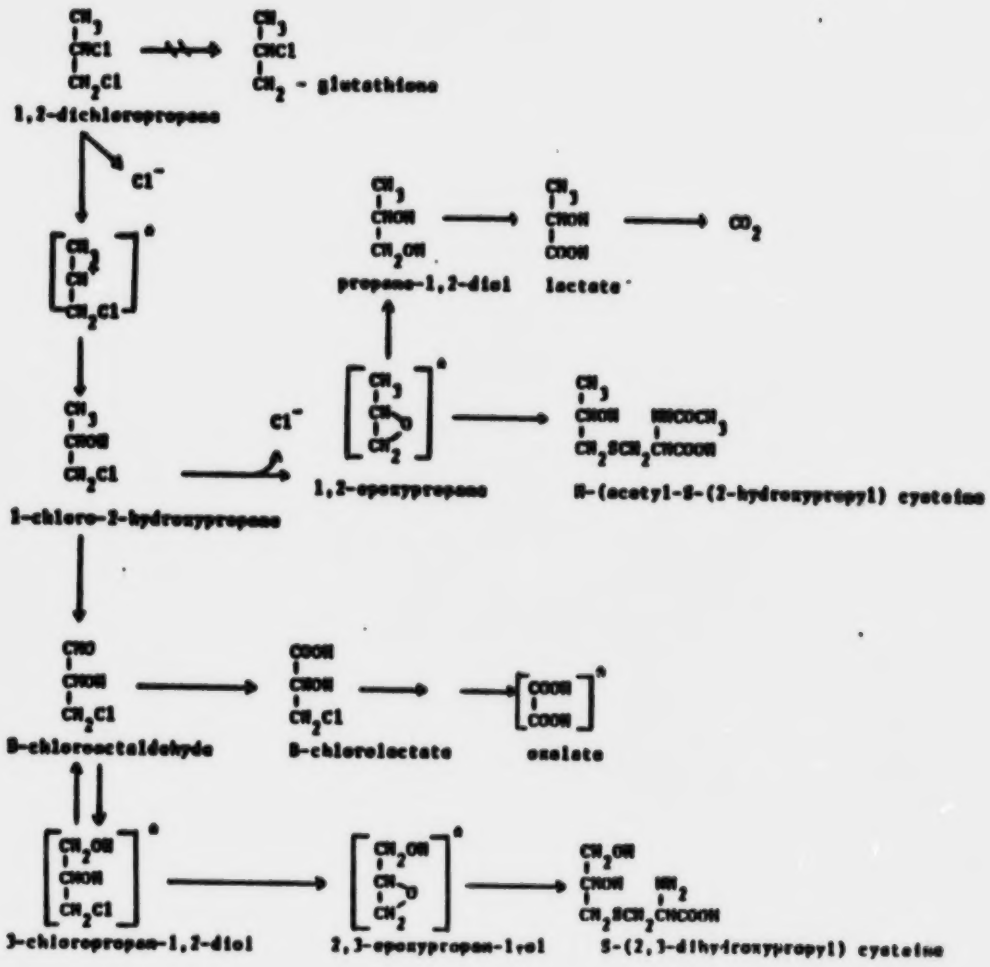

FIGURE III-1

Proposed Metabolic Pathway for 1,2-Dichloropropane in the Rat

*Compounds in brackets are proposed intermediates from Jones and Gibson (1980)

exhaled as [^{14}C] carbon dioxide. Jones and Gibson (1980) reported that at least 25-35% of a single oral dose of 1,2-dichloropropane (20 mg/kg) administered to male Sprague-Dawley rats was eliminated as N-acetyl-S-(2-hydroxypropyl) cysteine in the urine.

Summary

Although no specific data were located which quantified the absorption of 1,2-dichloropropane, it can be inferred from the study of Hutson et al. (1971) that this compound was almost completely absorbed from the gastrointestinal tract of rats. The metabolism of 1,2-dichloropropane has been studied *in vitro* and *in vivo*. [^{36}C]-1,2-Dichloropropane was dechlorinated in the presence of NADP, microsomes, and supernatant from rat liver (Van Dyke and Wineman, 1971). Upon incubation of 1,2-dichloropropane with hepatic 15,000 x g supernatant and reduced glutathione, no conjugates were formed. When Sprague-Dawley rats were dosed orally with 1,2-dichloropropane, N-acetyl-S-(2-hydroxypropyl) cysteine was isolated as a major urinary metabolite (Jones and Gibson, 1980). The proposed metabolic pathway for 1,2-dichloropropane (see Figure III-1) involves the oxidation of 1,2-dichloropropane to 1-chloro-2-hydroxypropane with ultimate production of the mercapturic acid, N-acetyl-S-(2-hydroxypropyl) cysteine. 1,2-Epoxypropane, derived from 1-chloro-2-hydroxypropane, is a proposed intermediary metabolite. Subsequently, this epoxide is hydrolyzed to propane-1,2-diol, a nontoxic compound which is further metabolized to lactate and CO_2 in the rat. B-Chlorolactate, derived from 1-chloro-2-hydroxypropane, was identified as a minor metabolite of 1,2-dichloropropane. This compound is further oxidized to oxalate. Finally, it has been suggested that 2,3-epoxypropan-1-ol is an intermediate in the metabolism from 3-chloropropan-1,2-diol to N-acetyl-S-(2,3-dihydroxypropyl) cysteine (Jones and Gibson, 1980).

1,2-Dichloro[1-^{14}C]propane was rapidly eliminated by rats dosed orally with 0.88 mg/rat (~4 mg/kg). Approximately 80-90% of the radioactivity was excreted in the urine, feces and expired air of rats within 24 hours of dosing (Hutson et al., 1971). Urinary and fecal excretion accounted for ~53% and 6%, respectively, of the radioactivity recovered after 96 hours. Approximately 19.3% of the administered radioactivity was recovered in the expired air of rats as [^{14}C]carbon dioxide; 23.1% was recovered as other volatile radioactivity, possibly as the parent compound.

IV. SOURCES OF HUMAN EXPOSURE - 1,2-DICHLOROPROPANE

This chapter summarizes the available data on use, environmental fate, and occurrence of 1,2-dichloropropane to characterize the potential for drinking water contamination. A more extensive discussion of the available information on 1,2-dichloropropane is presented in the draft document entitled "Occurrence of Synthetic Organic Chemicals in Drinking Water, Food, and Air" (USEPA 1987).

Humans may be exposed to 1,2-dichloropropane from a variety of sources, including drinking water, food, ambient and indoor air, occupational settings, and agricultural chemicals. This analysis of human exposure is limited to drinking water, food, and ambient air. Some individuals may receive additional exposure to 1,2-dichloropropane in their workplace or from using soil fumigants. Individual exposure to 1,2-dichloropropane will vary widely and will be dependent on where a person lives, works, and travels, and what a person eats. Intake of 1,2-dichloropropane will be affected by age, weight, and lifestyle.

The Exposure Estimates section of this chapter presents available information on the range of human exposure to and intake of 1,2-dichloropropane from drinking water, food, and ambient air. It is not possible to provide an estimate of the number of individuals experiencing specific exposures

from these three sources. However, this section provides insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

A. USE/ENVIRONMENTAL FATE

In 1980, 77 million pounds of 1,2-dichloropropane was produced (USITC 1981, as cited in USEPA 1985). The majority of this amount was used as an intermediate in the production of other chemicals. In 1982, approximately 20 million pounds of 1,2-dichloropropane were used as a component of a soil fumigant and 7 million pounds as a specialty solvent. Until 1982, 1,2-dichloropropane was used as a solvent in some consumer products (USEPA 1985).

While 1,2-dichloropropane can be released during production and transport, the major sources of release come from its uses as a soil fumigant and as a specialty solvent. Due to 1,2-dichloropropane's volatility, most releases to the environment will be to the atmosphere. However, significant amounts of 1,2-dichloropropane are released to ground water during soil fumigation and disposal of waste solvents.

Once released to the environment 1,2-dichloropropane tends to migrate to the air where it is readily degraded by photooxidation. 1,2-Dichloropropane released to surface

waters will tend to volatilize over time. Estimates of half-lives in surface water range from minutes to several months. 1,2-Dichloropropane is not expected to hydrolyze or biodegrade in surface waters. Adsorption to suspended and/or bottom sediments is also unlikely to be an important removal process for 1,2-dichloropropane in surface waters. Based on an estimated bioconcentration factor, 1,2-dichloropropane is not expected to undergo significant bioconcentration nor biomagnification in aquatic systems (USEPA 1987).

1,2-Dichloropropane released to soil is expected to migrate to ground water. Based on the classification system of Helling and Turner (1968) and cited in Hamaker (1975), 1,2-dichloropropane would be expected to be mobile in soils and to be moderately susceptible to leaching.

B. OCCURRENCE

Drinking Water

One Federal survey, the Ground Water Supply Survey, provides the most comprehensive sampling of public water supplies for estimating representative concentrations of 1,2-dichloropropane (USEPA 1983). Approximately 1,000 ground water supplies were sampled nationwide for 1,2-dichloropropane. The compound was detected in about 5 percent of the supplies

sampled, ranging from 0.21 to 120 ug/l. The quantitation limit was 0.2 ug/l.

Diet

1,2-Dichloropropane is widely used as a soil fumigant. This use could result in low levels of contamination of food grown in fumigated soils. Other soil fumigants, DBCP and EDB, have been detected at levels up to several thousand ug/kg in root crops. Because of this, EPA believes that 1,2-dichloropropane may be a low-level contaminant in food.

1,2-Dichloropropane was not included as an analyte in any of the available dietary studies. Consequently, monitoring data are unavailable to make estimates of actual levels in food.

Air

Brodzinsky and Singh (1982) compiled the most comprehensive atmospheric data available on 1,2-dichloropropane. In urban/suburban areas, a median concentration of 0.26 ug/m^3 was reported for 396 samplings. In source dominated areas, a median concentration of 0.55 ug/m^3 was reported for 26 samplings. No data were available for rural/remote areas. The low levels reported here are consistent with the limited releases and rapid photooxidation of 1,2-dichloropropane.

C. EXPOSURE ESTIMATES

The following table summarizes the exposure levels of 1,2-dichloropropane in drinking water, food, and air. The drinking water and air exposure levels are presented in ranges to reflect the uncertainty arising from the limited amount of monitoring data available. The upper bound for each route should be regarded as a general indicator of exposures if an individual was exposed to some of the higher reported levels. Air exposure levels are based on the monitoring data presented for urban/suburban areas which, in addition to comprising the majority of sampling areas, are more representative of typical inhalation levels. Due to the absence of data on 1,2-dichloropropane in food, dietary exposure could not be evaluated. The estimated daily intake levels were derived using several exposure assumptions, including an average adult intake of 2 liters per day of drinking water and 20 cubic meters of air per day.

Currently available information on the occurrence of 1,2-dichloropropane is insufficient to determine the national distribution of intake by any of the three routes of exposure. While the above table indicates that drinking water exposure can result in higher intakes than food or air, this should be taken only as a relative indication of the potential for intake from drinking water. The number of individuals who actually receive drinking water exposures that are greater

Table 1. Exposure Estimates for 1,2-Dichloropropane

Source	Reported Exposure Levels (low-high)	Estimated Daily Intake
Drinking Water	0-120 ug/l	0-240 ug/day
Diet	unknown	unknown
Air	0-0.26 ug/m3	5 ug/day

than dietary or inhalation exposures is unknown. EPA has no information on present levels of 1,2-dichloropropane in food and has little information on levels in indoor air; therefore, the relative significance of intakes by these routes for the population as a whole cannot be determined.

D. REFERENCES

Brodzinsky, R., and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Final Report. Prepared by: Atmospheric Science Center, SRI International. Prepared for: Environmental Sciences Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina.

Hamaker, J.W. 1975. Interpretation of soil leaching experiments. In: R. Hague and V.H. Freed (eds.). Environmental dynamics of pesticides. Plenum Press, New York, NY.

Helling, C.S., and B.C. Turner. 1968. Pesticide mobility: Determination by soil thin layer chromatography. Science: 162:562. As cited by Hamaker, J.W., In: R. Hague and V.H. Freed. 1975. Environmental dynamics of pesticides. Plenum Press, New York, NY.

USITC. 1981. U.S. International Trade Commission. Synthetic organic chemicals. U.S. Production and Sales, 1980. USITC Publication 1183. (as cited in USEPA 1985).

USEPA. 1983. U.S. Environmental Protection Agency. Ground Water Supply Survey, Summary of volatile organic contaminant occurrence data, U.S. Environmental Protection Agency, Office of Drinking Water, Technical Support Division.

USEPA. 1985. U.S. Environmental Protection Agency. 1,2-Dichloropropane; testing requirements. U.S. Environmental Protection Agency. Federal Register 51(174): 32079-32087.

USEPA. 1987. U.S. Environmental Protection Agency. Occurrence of pesticides in drinking water, food and air. Prepared by SAIC, McLean, Va. for Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC.

V. HEALTH EFFECTS IN ANIMALS

Acute and Short-Term Toxicity. Lethal oral doses of 1,2-dichloropropane are presented in Table V-1. Single dose oral LD_{50} values of 860, 2200 and 2000 mg/kg bw have been reported for mice (Merck Index, 1976), male rats (Smyth et al., 1969) and guinea pigs (Farm Chemicals Handbook, 1980), respectively. A single dose oral LD_{50} of 5000 mg/kg bw has been reported for dogs (Union Carbide Co., 1960), indicating that this species is less sensitive than rodents.

In a range-finding study that was conducted as part of an NTP carcinogenesis bioassay, groups of 5 F344/N rats and 5 $B6C3F_1$ mice of each sex were administered reagent grade 1,2-dichloropropane (~99.4% pure) in corn oil by gavage at doses of 0, 125, 250, 500, 1000 or 2000 mg/kg bw/day for 14 consecutive days followed by 1 day of observation (see Table V-1; NTP, 1986). The rats and mice were ~6 weeks old at the beginning of the study; necropsies were performed on all animals; however, histopathological examinations were not conducted on any of the tissues.

All of the high-dose (2000 mg/kg bw) rats died during the study, and the mean terminal body weights were reduced in the 500 and 1000 mg/kg bw male (14%) and 1000 mg/kg bw female (15%) groups (NTP, 1986). Renal medullae were found to be red in 4/5 males and 5/5 females that were administered 2000 mg/kg bw 1,2-dichloropropane, but this effect was not found in rats that received lower (nonlethal) doses. In the mouse study all males at the 1000 and 2000 mg/kg bw dose levels and all females at 2000 mg/kg bw died, and 3/5 males at 500 mg/kg bw and 4/5 females at 1000 mg/kg bw also died.

TABLE V-1

Acute and Short-Term Toxic Effects of 1,2-Dichloropropane

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/Wistar	male/5	90-120 g/ 4-5 weeks	NR	gavage/NR	2200 mg/kg	single dose	LD_{50}	Smyth et al., 1969
Rat/F344/N	male/5	~114 g/ 6 weeks	~99.4%*	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days	100% mortality for males and females at 2000 mg/kg dose level; terminal body weight decreased 14% in 1000 and 500 mg/kg males, 10% in 250 and 125 mg/kg males, and 15, 8, 5 and 2% in 1000, 500, 250 and 125 mg/kg females, respectively, relative to controls; renal medullae were red in 4/5 males and 5/5 females receiving 2000 mg/kg; histopathological examinations were not conducted.	NTP, 1986
	female/5	~96 g/6 weeks	~99.4%*	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days		
Rat/Sprague-Dawley	NR/39	150-200 g/NR	NR	inhalation/NR	2200 ppm (~10,400 mg/m³)	4 or 7 hours (single exposure)	No significant changes in livers of rats exposed 4 hours; some degeneration of the liver, kidney and adrenals in rats exposed for 7 hours; hemosiderin was seen in the spleen of rats exposed for 7 hours.	Highman and Heppel, 1946
Rat/Sprague-Dawley	NR/5-6 (each exposure duration)	150-200 g/NR	NR	inhalation/NR	2200 ppm (~10,400 mg/m³)	7 hours/day for 2-5 exposures	Rats killed after 2 exposures showed marked diffuse fatty degeneration of the liver and centrilobular necrosis; rats killed after 3 exposures showed advanced necrosis and fatty degeneration bordering necrotic area; rats killed after 4 exposures showed a narrow centrilobular cellular zone composed chiefly of monocytes with few necrotic cells and surrounded by a narrow zone of fatty generation; rats killed after 5 exposures showed either no change or few centrilobular lymphoid cells and monocytes with a few marginal fat-laden liver cells; some renal fat was seen in rats exposed 2, 3 or 4 times, but not in rats exposed 5 times; adrenal cortex fat was reduced after 2 and 3 exposures; hemosiderin was seen in the spleen of rats exposed 4 or 5 times.	Highman and Heppel, 1946

01920

04/17/87

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/NR	NR/20	NR/NR	reagent grade*	inhalation/NA	10,400 mg/m³ (2200 ppm)	7 hours/day, 5 days/week for 5-8 exposures	Gross incoordination, crusting around the nose, rough fur, coarse breathing; 5/20 died after 5 exposures; 3/8 died after 8 exposures; visceral congestion, coagulation necrosis of liver with slight centrilobular fatty degeneration; lipoid depletion of the adrenal cortex; splenic hemosiderosis only significant effect 2-4 weeks following exposure.	Heppel et al., 1946
Rat/Albino	NR	NR/NR	NR	inhalation/NA	2000 ppm (~9240 mg/m³)	8 hours (single exposure)	3/6 died	Smyth et al., 1969
Rat/NR	NR/12	NR/NR	reagent grade*	inhalation/NA	6900 mg/m³ (~1600 ppm)	7 hours (single exposure)	3/12 died; mild incoordination at end of exposure only sign of intoxication; histopathological examination not performed.	Heppel et al., 1946
Rat/NR	NR/13	NR/NR	reagent grade*	inhalation/NA	6900 mg/m³ (~1600 ppm)	7 hours/day for 5 exposures	No deaths; weight loss that was regained after conclusion of exposure; histopathological examinations not performed.	Heppel et al., 1946
Rat/CD-1	male/NR	200-250 g	>99%	inhalation/NA	1000 ppm (~4620 mg/m³)	4 hours (single exposure)	No change in serum glucose-6-phosphatase level; significant increase in SGOT, SGPT and OCT activities 24 and 48 hours after exposure.	Drew et al., 1978

01920

06/27/84

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/white	male/NR	200-240 g/NR	NR	inhalation/NA	1000 or 2000 mg/m³ (~216 or 433 ppm, respectively)	7 days, continuous	Histostructural damage to the liver, reduced hepatic enzymic activity, reduction in content of ribonucleoproteins in centrilobular sections accompanied by microcirculatory disturbances and increased vascular permeability; hyperplasia and hypertrophy of peripheral sections of lobules; increase in number of unicellular polypoidal hepatocytes; histostructural changes in the kidney with suppression of oxidation enzymes and phosphomonoesterases; unspecified changes in blood catalase and cholinesterase activities; no effect on blood cell count, hemoglobin or body weight; results inadequately reported.	Sidorenko et al., 1976
Rat/NR	NR/NR	NR/NR	NR	inhalation/NA	1 or 2 mg/m³ (~0.22 or 0.43 ppm, respectively)	7 days, continuous	Extensive hemorrhages in lungs with desquamation and destruction of bronchial, bronchiolar and alveolar epithelium; swollen and vacuolized endothelium of arteriole and venulae; hypertrophied muscular wall; inhibition of ATPase, acid phosphatase and alkaline phosphatase in lung parenchyma and bronchi; Russian study reported as an abstract.	Bonashevskaya, et al., 1978
Mouse/NR	NR/NR	NR/NR	NR	oral/NR	860 mg/kg	single dose	LD_{50}	Merck, 1976

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Mouse/B6C3F1	male/5	~22 g/6 weeks	~99.4%[a]	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days	All male mice at 1000 or 2000 mg/kg dose level and all female mice at 2000 mg/kg dose level died; 3/5 males at 500 mg/kg dose level and 4/5 females at 1000 mg/kg dose level died; terminal body weights were not affected adversely but were slightly higher than body weights of controls; renal medullae were red in all mice receiving 2000 mg/kg, in 3/5 males receiving 500 mg/kg, in 3/5 females receiving 1000 mg/kg and in 1/5 females in each of the 125, 250 and 500 mg/kg groups; histopathological examinations were not conducted.	NTP, 1986
	female/5	~18 g/6 weeks	~99.4%[a]	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days		
Mouse/NR	NR/11	NR/NR	reagent grade[a]	inhalation/NA	10,400 mg/m³ (~2200 ppm)	7 hours (single exposure)	Excitation; hyperactivity; gross incoordination; 100% mortality; histological examinations not performed.	Heppel et al., 1946
Mouse/NR	NR/10	NR	NR	inhalation/NA	6500 mg/m³ (~1500 ppm)	2 hours	3/10 died with fatty degeneration, centrilobular congestion and necrosis of the liver.	Heppel et al., 1946
	NR/22	NR	NR	inhalation/NA	6500 mg/m³ (~1500 ppm)	4 hours	22/22 died	
Mouse/NR	NR/81	NR/NR	NR	inhalation/NA	4400 mg/m³ (~1000 ppm)	0-4 hours	Mortality after 1, 2, 2.5, 3 and 4 hours of exposure was 0/11, 1/11, 3/22, 8/11 and 26/26, respectively. Fatty degeneration and centrilobular congestion of liver and slight fatty degeneration of kidney in 6/6 and 3/6 examined, respectively.	Heppel et al., 1946
Mouse/C57	NR/16	NR	NR	inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 1-12 exposures	Mortality with liver and kidney histologic damage as detailed in the Subchronic Toxicity Section and Table V-2.	Heppel et al., 1948

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Mouse/NR	NR/NR	NR/NR	NR	inhalation/NA	26.0, 22.0, 17.5, 12.6 or 4.8 mg/ℓ	single exposure, duration not stated	General agitation, decreased coordination, sluggishness, amyotonia, sporadic clonic spasms, loss of righting reflex; onset of effects reportedly dose-related; inadequately reported results.	Sidorenko et al., 1976
Guinea pig/ NR	NR/NR	NR/NR	NR	oral/NR	2000 mg/kg	single dose	LD_{50}	Farm Chemicals Handbook, 1980
Guinea pig/ NR	NR/39	600-800 g/NR	NR	inhalation/NA	2200 ppm (~10,400 mg/m³)	4 or 7 hours (single exposure)	Fatty degeneration of the liver and kidneys; extensive coagulation and focal hemorrhagic necrosis of the adrenal cortex; congestion with hemorrhage and parenchymatous degeneration of the adrenal medulla.	Highman and Heppel, 1946
Guinea pig/ NR	NR/4-5 (each exposure duration)	600-800 g/NR	NR	inhalation/NA	2200 ppm (~10,400 mg/m³)	7 hours/day for 2-4 exposures	Effects similar to single 2200 ppm exposure.	Highman and Heppel, 1946
Guinea pig/ NR	NR/16	NR/NR	reagent grade*	inhalation/NR	2200 ppm (~10,400 mg/m³)	7 hours/day for 5 exposures	Lacrimation followed by conjunctival swelling; weight loss; rough fur; coarse breathing; 11/16 died by 5th exposure; fatty degeneration of the liver (with some centrilobular necrosis) and kidneys; necrosis of adrenal cortex; some splenic hemosiderosis and pulmonary congestion.	Heppel et al., 1946
Guinea pig/ NR	NR/6	NR/NR	reagent grade*	inhalation/NR	6900 mg/m³ (~1600 ppm)	7 hours (single exposure)	No signs of intoxication; histological examinations not conducted.	Heppel et al., 1946
Guinea pig/ NR	NR/10	NR/NR	reagent grade*	inhalation/NR	6900 mg/m³ (~1600 ppm)	7 hours/day for 5 exposures	Weight loss that was regained after exposure; no mortality.	Heppel et al., 1946
Rabbit/NR	NR/4	NR/NR	NR	inhalation/NA	10,400 mg/m³ (~2200 ppm)	7 hours/day, 5 days/week for 5-8 exposures	2 died after 2nd exposure; evidence of degenerative changes in the liver and kidney.	Heppel et al., 1946

01920

06/27/84

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rabbit/NR	NR/2	NR/NR	reagent grade*	inhalation/NA	6900 mg/m³ (~1600 ppm)	7 hours (single exposure)	No signs of intoxication.	Heppel et al., 1946
Rabbit/NR	NR/2	NR/NR	reagent grade*	inhalation/NA	~1600 ppm (6900 mg/m³)	7 hours/day, for 5 exposures	No signs of intoxication; 1 rabbit was histologically examined and showed evidence of focal interstitial pneumonitis, splenic hemosiderosis and slight fatty degeneration of liver and kidney.	Heppel et al., 1946
Rabbit/ Albino	male/4	2.5-3.5 kg/NR	NR	dermal/NR	1000 mg/kg	single dose	LD_{50}	Smyth et al., 1969
Dog/NR	NR/11	NR/NR	NR	gavage/NR	0.2-0.5 mL/kg (~230-580 mg/kg)	single dose	Signs of central nervous system toxicity, histopathologic effects primarily in the liver (congestion, hemorrhage, slight cloudy swelling and fatty degeneration); other effects in the kidney (congestion), GI tract (hemorrhage, irritation) and lung (congestion, hemorrhage).	Wright and Schaffer, 1932
Dog/NR	NR/2	NR/NR	NR	gavage/NR	3 or 5 mL/kg (~3480 or 5797 mg/kg)	single dose	Dog dosed with 5797 mg/kg died with severe congestion in the liver, kidney and lungs. 3480 mg/kg not lethal to other dog, but histological examination not conducted.	Wright and Schaffer, 1932

*Reagent grade 1,2-dichloropropane that contained 0.24% toluene

NA = Not applicable; NR = Not reported

01920

06/27/84

The mean terminal body weights of the surviving treated mice were not adversely affected, but rather were slightly higher than terminal body weights of the controls. At necropsy renal medullae were red in all mice of both sexes at 2000 mg/kg bw, in 3/5 males at 500 mg/kg bw, in 3/5 females at 1000 mg/kg bw, and in 1/5 females in each of the 125, 250 and 500 mg/kg bw groups. Treatment-related pathologic effects other than red renal medullae were not noted in the rats and mice, but again histopathologic examinations were not performed.

In an early report which evaluated the antihelmintic properties of different chlorinated hydrocarbons, dogs were orally treated with 1,2-dichloropropane (Wright and Schaffer, 1932). Eleven dogs (strain and sex not specified) were given single doses of 0.2-0.5 mL 1,2-dichloropropane/kg bw (230-580 mg/kg bw) by stomach tube and examined for gross pathologic effects after 3-4 days; microscopic examinations of the liver and kidneys were conducted on 5 of the 11 dogs. Signs of intoxication were indicative of CNS effects and included incoordination, loss of balance, unsteady gait and glazed eyes. Gross and microscopic pathological changes in the liver (e.g., congestion, hemorrhage, slight cloudy swelling and fatty degeneration) were evident in all of the dogs. Renal effects (e.g., congestion, gross discoloration) were found in 4/11 dogs and appeared to be more pronounced at the high-dose (cloudy swelling and fatty infiltration described in 1/2 dogs administered 580 mg/kg bw). Local effects on the gastrointestinal tract (e.g., hemorrhage, irritation) were apparent in 6/11 treated dogs. Oral administration of 3.0 mL/kg bw (~3480 mg/kg bw) 1,2-dichloropropane to one dog did not produce signs of intoxication, but similar administration of 5.0 mL/kg bw (~5797 mg/kg bw) to another dog was fatal; severe congestion was

observed in the liver, kidney and lungs of the dog dosed with 5797 mg/kg; a necropsy was not performed on the dog exposed to 3480 mg/kg bw.

Inhalation of concentrated vapor of 1,2-dichloropropane (level undetermined) for 10 minutes was the maximum exposure at which no deaths occurred among exposed rats (Smyth et al., 1969). An 8-hour exposure to 2000 ppm (~9240 mg/m³) dichloropropane caused 50% mortality (3/6) among exposed rats (strain not specified) (Smyth et al., 1969). Of 20 rats exposed to 10,400 mg/m³ (~2200 ppm) 1,2-dichloropropane, 5 died after 5 daily 7-hour exposures and 3/8 died after 8 exposures (Heppel et al., 1946); mortality on days 6 and 7 of exposure was not explicated, but total mortality was apparently 15/20. Significant histological effects were not observed in Sprague-Dawley rats that were exposed to 2200 ppm for 4 hours, but some degenerative changes were noted in the liver, kidney and adrenals of rats exposed for 7 hours (Highman and Heppel, 1946). Repeated daily exposure to 2200 ppm 1,2-dichloropropane (7 hours/day, 5 days/week) produced marked degenerative changes in these organs after 2-8 exposures (Highman and Heppel, 1946; Heppel et al., 1946) (see Table V-1). Signs of intoxication included gross incoordination, crusting around the nose, coarse breathing and roughening of the fur (Heppel et al., 1946). Heppel et al. (1946) also reported that no mortality occurred among 13 rats (strain not specified) exposed to 6900 mg/m³ (~1600 ppm) 1,2-dichloropropane for 5 consecutive 7-hour exposures; weight loss was noted but necropsies were not performed. In an inhalation study with male CD-1 rats, Drew et al. (1978) determined that serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and ornithine carbamyl transferase (OCT) activities were increased after a single 4-hour exposure to 1000 ppm (4620 mg/m³) 1,2-dichloropropane, but no change in glucose-6-phosphatase was found.

Sidorenko et al. (1976) exposed an unspecified number of white male rats to 1000 or 2000 mg/m³ (~216 or 432 ppm, respectively) 1,2-dichloropropane by inhalation continuously for 7 days (see Table V-1). A number of inadequately described effects were reported in the liver (histostructural and vascular damage, reduced enzyme activities and reduced ribonucleoprotein content in the centrilobular portion, hyperplasia and hypertrophy in the peripheral portion and increased number of polyploidal hepatocytes) and kidneys (histostructural damage, reduced activity of oxidation enzymes and phosphomonoesterase). Unspecified changes in blood catalase and cholinesterase activities were also reported, but blood cell count, hemoglobin content and body weights were apparently not altered by treatment. In an English abstract of a Soviet study (Bonashevskaya et al., 1978), rats were exposed by inhalation to 1 or 2 mg/m³ (0.22 or 0.43 ppm) 1,2-dichloropropane for 7 days (presumed continuous). Extensive pulmonary effects were reported that included hemorrhage and destruction of bronchial, bronchiolar and alveolar epithelium, swollen and vacuolized endothelium of pulmonary arterioles and venules, and reduced ATPase, acid phosphatase and alkaline phosphatase levels. It should be emphasized, however, that the design and results of the above studies were inadequately reported, and that additional data were not available.

Mice appear to be more sensitive than rats with 100% mortality reported following exposure to 4400-10,400 mg/m³ (~1000-2200 ppm) 1,2-dichloropropane for 4-7 hours (Heppel et al., 1946) (see Table V-1). Mortality among mice exposed to 1000 ppm for 1, 2, 2.5, 3 or 4 hours was 0/11, 1/11, 3/22, 8/11 or 26/26, respectively. Degenerative changes in the liver and kidney were the primary effects of exposure, but the adrenal degeneration

seen in rats was not noted in mice. Repeated exposure to 400 ppm 1,2-dichloropropane (7 hours/day, 5 days/week for 1-12 days) produced mortality in mice with histologic liver and kidney damage as detailed in the Subchronic Toxicity Section and Table V-2 (Heppel et al., 1948). Sidorenko et al. (1976) exposed mice to single vapor exposures of 26.0, 22.0, 17.5, 12.6 or 4.8 mg/ℓ 1,2-dichloropropane for an unspecified length of time and observed general agitation, decreased coordination, sluggishness, amyotonia, sporadic clonic spasms and loss of righting reflex. The onset of these effects was reported to be dose-related.

Highman and Heppel (1946) also exposed guinea pigs to 2200 ppm (~10,400 mg/m³) 1,2-dichloropropane for single 4- or 7-hour exposures, or for 2, 3 or 4 consecutive daily 7-hour exposures. Histological effects observed among animals treated at this level included fatty degeneration of the liver and kidney, extensive coagulation and focal hemorrhagic necrosis of the adrenal cortex and congestion of the adrenal medulla. Guinea pigs exposed to 2200 ppm (~10,400 mg/m³) 7 hours/day for five exposures experienced lacrimation followed by conjunctival swelling, weight loss, roughening of the fur and coarse breathing. Of the 16 guinea pigs exposed on this schedule, 11 died by the fifth exposure. Guinea pigs exposed repeatedly to 6500 mg/m³ (~1500 ppm) 1,2-dichloropropane (7 hours/day, 5 days/week) exhibited drowsiness, decreased growth, 28% mortality (5/18) after 6 or 11 exposures, and subcortical fibrosis of the adrenals (Subchronic Toxicity Section and Table V-2) (Heppel et al., 1946). Repeated exposures to 1000 or 400 ppm 1,2-dichloropropane did not appear to be lethal for guinea pigs (see Table V-2) (Heppel et al., 1946, 1948); subcortical fibrosis was a marked histological effect of the 1000 ppm exposures, but minimal histological effects were elicited by exposure to 400 ppm.

TABLE V-2

Effects of Subchronic Exposure of Experimental Animals to 1,2-Dichloropropane

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/F344/N	male/10	~136 g/ 7-8 weeks	~99.4%[a]	gavage/ corn oil	0, 60, 125, 250, 500 or 1000 mg/kg bw	5 days/week for 13 weeks	All males and females at 1000 mg/kg dose level died and 5/10 males receiving 500 mg/kg died; mean terminal body weights were depressed 16% in males and 8% in females at 500 mg/kg; centrilobular congestion of the liver occurred in 5/10 males and 2/10 females at 1000 mg/kg level; hepatic fatty changes and centrilobular necrosis were observed in 2/10 females at 1000 mg/kg dose level; histopathological examinations were conducted only in the 0, 500 and 1000 mg/kg groups.	NTP, 1986
	female/10	~100 g/ 7-8 weeks	~99.4%[a]	gavage/ corn oil	0, 60, 125, 250, 500 or 1000 mg/kg bw	5 days/week for 13 weeks		
Rat/NR	NR/NR	NR/NR	NR	oral/NR	14.4 or 360 mg/kg bw	30 days	Increase in blood serum cholesterol, beta-lipoproteins and gamma globulin by day 10; serum pseudocholinesterase inhibited by day 20; fructose-1-monophosphate adolase, alanine transaminase and asparagine transaminase were stimulated by day 20; analine transaminase was inhibited by day 30; results reported in an abstract.	Kurysheva and Ekshtat, 1975
Rat/NR	male/13, female/5	162 g/NR	NR[b]	inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 35 exposures	8/18 died after 1-35 exposures[c], 1/14 controls died; reversible unsteadiness; growth adversely affected, but not quantified; centilobular fatty degeneration in livers of 2/9 examined; "several" showed increased hemosiderin in spleen.	Heppel et al., 1946

01920

04/17/87

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/Wistar	male/5, female/22	215 g/NR	NR[b]	Inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day 5 days/week for 97 exposures	9/27 died after 6-32 exposures, 1/18 controls died; depressed weight apparent result of decreased food consumption; signs of intoxication (rough fur, crusty eyes, coarse breathing, weakness) noted before death.[d]	Heppel et al., 1946
Rat/Sprague-Dawley	male/12	210 g/NR	NR[b]	Inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day 5 days/week for 47 exposures	12/12 died after 10-47 exposures, 0/13 controls died; more sensitive than Wistar strain; signs of intoxication before death (see Wistar response).[d]	Heppel et al., 1946
Rat/Sprague-Dawley	male/6	120 g/NR	NR[b]	Inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day, 5 days/week for 93 exposures	4/6 died after 17-59 exposures, 0/6 controls died; more sensitive than Wistar strain; signs of intoxication before death (see Wistar response).[d]	Heppel et al., 1946
Rat/NR	male/26, female/23	260 g/NR	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 140 exposures	3/49 died after 108-134 exposures, 0/30 controls died; depressed weight gain, but no signs of toxicity; histological examination of 75 rats after 3-140 exposures showed slight hemosiderin deposition in the liver.	Heppel et al., 1948
Mouse/B6C3F1	male/10	~24 g/ 15 weeks	~99.4%[a]	gavage/ corn oil	0, 30, 60, 125, 250 or 500 mg/kg bw	5 days/week for 13 weeks	One male at 60 mg/kg dose level died and one female at 500 mg/kg dose level died; mean terminal body weights were depressed 5, 1.1, 1.4 and 4.4% in the 500, 125, 60 and 30 mg/kg males, respectively, and 3.6, 3.2, 0.4 and 1.1% in the 500, 250, 60 and 30 mg/kg females, respectively; compound-related histopathologic effects were not observed, but only 0 and 500 mg/kg groups were examined.	NTP, 1986
	female/10	~22 g/ 15 weeks	~99.4%[a]	gavage/ corn oil	0, 30, 60, 125, 250 or 500 mg/kg bw	5 days/week for 13 weeks		

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Mouse/C57	NR/16	NR	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 1-12 exposures	Mortality data incompletely reported; slight fatty degeneration in liver of 5/8 that died or were killed after the first exposure; slight fatty degeneration of kidney in 1/2 killed after 2 exposures; histological effects not noted in other exposed or 5 controls.	Heppel et al., 1948
Mouse/C3H	NR/80	NR/NR	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	4-7 hours/day, 5 days/week for 37 exposures	"most" of the mice died during the study; of an unspecified number that received 14-28 exposures, 9 showed liver congestion and fatty degeneration, 7 showed liver centrilobular necrosis, and 6/8 showed kidney fatty degeneration. Hepatomas also occurred.	Heppel et al., 1948
Guinea pig/ NR	male/7, female/11	588 g/NR	NR[b]	Inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 39 exposures	5/18 died after 6 or 11 exposures, 1/25 controls died; drowsiness; growth adversely affected but not quantified; subcortical fibrosis of adrenals in 9/9 examined, but no significant hepatic effects.	Heppel et al., 1946
Guinea pig/ NR	male/12	800 g/NR	NR[b]	Inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day, 5 days/week for 126 exposures	3/12 died after 22-97 exposures, 1/14 controls died. Subcortical fibrosis of adrenals in 9/9 examined after 126 exposures.	Heppel et al., 1946
Guinea pig/ NR	male/2, female/14	640 g/young	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 134 exposures	3/16 died after 63-111 exposures, 8/24 controls died; minimal hemosiderin deposition in the spleen and adrenals and minimal fatty changes in the liver, kidney and heart[c].	Heppel et al., 1948
Guinea pig/ NR	male/10, female/6	1072 g/mature	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 134 exposures	4/16 died after 3-97 exposures, 4/18 controls died. Minimal histological effects as described for young guinea pigs above[c].	Heppel et al., 1948

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rabbit/NR	male/1, female/3	2270 g/NR	NR[b]	inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 39 exposures	1/4 died after 26 exposures 0/4 controls died; no adverse effects on appearance or weight gain; no significant histological lesions in 3/3 examined.	Heppel et al., 1946
Rabbit/NR	male/4	3.7 kg/NR	NR[b]	inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day, 5 days/week for 126 exposures	0/4 died, 0/4 controls died; no significant histological lesions; normal blood cell count and hemoglobin[f].	Heppel et al., 1946
Dog/NR	NR/1	NR/NR	NR[b]	inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, for 6 exposures	No obvious "ill effects."	Heppel et al., 1946
Dog/NR	NR/98	3.4-9.5 kg/NR	NR[b]	inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 55 exposures (2 pups) or 128 exposures (2 pups and 5 adults)	3/5 adults and 1/4 puppies died after 27-28 (adult) and 96 (puppy) exposures; 0/3 adult and 0/1 pup controls died; fatty degeneration of liver and convoluted tubules of kidney in the 4 dogs that died; fatty degeneration of heart and adrenal cortex in 2/4 that died; no significant histopathological effects in survivors; blood count and hemoglobin[f] and liver and kidney function tests[h] normal in dead and surviving dogs.	Heppel et al., 1946
Dog/NR	female/5	9.2 kg/NR	NR[b]	inhalation/NA	400 ppm (1850 mg/m³)	7 hours/day, 5 days/week for 128 exposures	0/5 died, 0/5 control died; slight hemosiderosis in the spleen in 5/5, scattered granulomatous lesions in kidney of 2/5.	Heppel et al., 1948

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/NR	NR/20	NR/NR	NR	Inhalation/NA	9 mg/m³ (1.9 ppm)	94 days	Disruption of CNS function, blood enzyme activity, DNA synthesis by the liver and biological oxidation in the liver, lungs and adrenals; results reported in an abstract.	Tsulaya et al., 1977

[a]Reagent grade 1,2-dichloropropane that contained 0.24% toluene.

[b]A commercial product with unknown precise composition was used; it was noted that the results of "precision distillation" of this product in a 4-foot fractionating column indicated that it "probably contained a considerable percentage of other isomers."

[c]Three of the rats were sacrificed after 10 exposures.

[d]Four rats of unspecified strain that died after 7 exposures showed moderate to marked fatty degeneration of the liver, kidneys and heart and splenic hemosiderosis. 18 rats of unspecified strain that were killed after 23-97 exposures showed moderate to marked splenic hemosiderosis, but 16 controls killed at the same time showed slight to moderate splenic hemosiderosis.

[e]12 unspecified guinea pigs were killed immediately after 134 exposures and compared histologically with 17 control animals of the same age. Seven unspecified guinea pigs were killed 6-8 months after the completion of 134-137 exposures and compared with 5 controls.

[f]Red and white cell counts, differential counts and hemoglobin determination were conducted at intervals of ~1 month on all exposed dogs and rabbits exposed to 1000 ppm, and on 4 control rabbits and 3 control dogs.

[g]Five adults and four puppies

[h]Determination of prothrombin time, bromsulfalein excretion, total plasma proteins, A/G ratio, plasma N.P.N. and serum phosphatase were done on "one or two occasions" for each of the 3 adult dogs that died, but some of the determinations were made "within 6 days of death." The 2 surviving adult dogs were tested for bromsulfalein excretion, serum phosphatase level, prothrombin time, total plasma protein, albumin, nonprotein nitrogen, sugar, acetone, bile pigments and abnormal cellular constituents. Determinations of prothromin time, bromsulfalein excretion, serum phosphatase, icterus index, total protein, albumin and nonprotein nitrogen were conducted on the 4 exposed and 1 control puppy.

NA = Not applicable; NR = Not reported

01920

06/27/84

Treatment-related effects were not observed in rabbits exposed by inhalation to 4400 mg/m³ (~1000 ppm) or 6900 mg/m³ (~1600 ppm) 1,2-dichloropropane for 7 hours (Heppel et al., 1946) (see Table V-1). At 2200 ppm (~10,400 mg/m³), 50% mortality (2/4) was observed after 2 exposures and degenerative changes were apparent in the liver and kidneys.

Subchronic Toxicity. Subchronic oral toxicity studies were conducted by NTP (1986) to determine the doses to be used in a chronic carcinogenicity bioassay of 1,2-dichloropropane. In these range-finding studies, groups of 10 F344/N rats and 10 $B6C3F_1$ mice of each sex were gavaged with reagent grade 1,2-dichloropropane (~99.4% pure) in corn oil, 5 days/week for 13 weeks at doses of 0, 60, 125, 250, 500 or 1000 mg/kg bw (rats) and 0, 30, 60, 125, 250 or 500 mg/kg bw (mice). Body weight measurements and clinical examinations were conducted weekly; necropsies were performed on all animals. Comprehensive histopathological examinations were conducted on the control, 500 and 1000 mg/kg bw groups of rats, and on the control and 500 mg/kg bw groups of mice.

All of the male and female rats in the 1000 mg/kg bw (714.3 mg/kg bw/day) dose groups and 5 of 10 males in the 500 mg/kg bw (357 mg/kg bw/day) dose groups died (see Table V-2) (NTP, 1986). Terminal mean body weights were depressed 16% in males and 8% in females that received 500 mg/kg bw (375 mg/kg bw/day). Non-neoplastic hepatic lesions were found in the high-dose (1000 mg/kg bw) rats of both sexes; these included centrilobular congestion (5/10 males, 2/10 females) and fatty changes and centrilobular necrosis (2/10 females). Treatment-related mortality, terminal body weight depression or histopathological effects were not described in the mice of either sex (see Table V-2).

The only other subchronic oral toxicity data that are available were reported in an English abstract of a Soviet study. Kurysheva and Ekshtat (1975) administered daily doses of 14.4 or 360 mg 1,2-dichloropropane/kg bw to an unspecified number of rats for 30 days, but the method and frequency of oral administration were not stated. Blood serum cholesterol, beta-lipoproteins and gamma globulin levels were reportedly increased by day 10, serum pseudocholinesterase was inhibited by day 20, fructose 1-monophosphate aldolase, alanine transaminase and asparagine transaminase were stimulated by day 20, and alanine transaminase was inhibited by day 30. Additional information regarding the design or results of this study were not provided.

Information on the subchronic inhalation toxicity of 1,2-dichloropropane is available from the studies of Heppel et al. (1946, 1948). In these studies, rats, mice, guinea pigs and rabbits were exposed for 7 hours daily, "nearly always" 5 days/week for different durations to concentrations of 10,400 mg/m³ (~2200 ppm), 6500-6900 mg/m³ (~1500-1600 ppm), 4400 mg/m³ (~1000 ppm) and ~1850 mg/m³ (400 ppm) 1,2-dichloropropane. A limited number of dogs were similarly exposed to 1500, 1000 and 400 ppm 1,2-dichloropropane and unexposed control animals were employed at each dose level for all species. The design and results of these studies are summarized in Table V-2. Signs of intoxication were described and autopsies were reportedly conducted on all of the exposed and "many" of the control animals, but it should be noted that the results of gross and histological tissue examinations were ambiguous and reported incompletely, that the extent of histological examination was unclear, and that particularly small numbers of rabbits and dogs were exposed at each dose level. Blood cell counts and hemoglobin determinations were conducted on all rabbits and dogs exposed to

1000 ppm 1,2-dichloropropane, and liver and kidney function tests were conducted on selected dogs exposed to 1000 ppm. The 1,2-dichloropropane used in these experiments, however, was a commercial product that "probably contained a considerable percentage of other isomers."

As detailed in the Acute Toxicity Section, exposure of rats, mice, guinea pigs and rabbits to 2200 ppm 1,2-dichloropropane (7 hours/day, 5 days/week) produced signs of acute toxicity in all these species with mortality after 5 or 8 exposures (rats, guinea pigs) or 2 exposures (rabbits) (Heppel et al., 1946); mice were the most sensitive with 10/11 dying during the first exposure. Rats, guinea pigs and rabbits that were exposed to ~1600 ppm 1,2-dichloropropane for 5 consecutive days survived the exposures (except for 1 of 2 rabbits) and appeared only to exhibit minimal signs of toxicity (see Acute Toxicity Section), but mice were not tested at this dose level. Exposure to ~1500 ppm for 35-39 exposures produced signs of CNS depression (e.g., unsteadiness, drowsiness), mortality starting in the first and second weeks of exposure and growth depression in rats and guinea pigs. Rabbits were generally unaffected and all mice died after a single 2- to 4-hour exposure. Similar results were obtained at ~1000 ppm with these species and with dogs, except that the responses were less marked and deaths occurred somewhat later in the experiment. The mice, as with the higher concentrations, were killed by a single 2-4 hour exposure to ~1000 ppm 1,2-dichloropropane. Animals that died from the exposures to ~1000-2000 ppm 1,2-dichloropropane had histological evidence of liver (fatty degeneration, coagulation necrosis) and kidney (fatty degeneration) damage, and the adrenal cortex in guinea pigs showed fibrosis. With the exception of splenic hemosiderosis (rats) and adrenal subcortical fibrosis (guinea pigs), survivors did not appear to exhibit significant histological effects of

exposure. The hematological, liver function and kidney function analyses of the dogs and rabbits did not indicate significant treatment-related effects.

In the second study, rats, guinea pigs and dogs received 128-140 seven-hour exposures (5 days/week) of 400 ppm 1,2-dichloropropane (see Table V-2) (Heppel et al., 1948). The only significant adverse effect in these three species that was attributable to exposure was a decreased weight gain in the rats (~10% in males, ~15% in females). In the same study, mice were similarly exposed to 400 ppm 1,2-dichloropropane 7 hours/day, 5 days/week. Mortality data were incompletely reported, but C57 and C3H mice died as a result of exposure to 400 ppm 1,2-dichloropropane; the C57 mice started dying after the first exposure. C57 mice that died or were killed after one to two 7-hour 400 ppm exposures showed slight fatty degeneration of the liver and kidneys. These effects appeared to be more severe in C3H mice receiving the 14-28 4- to 7-hour exposures resulting in moderate to severe congestion, fatty degeneration of the liver and extensive centrilobular coagulation necrosis of the liver, and slight to moderate fatty degeneration of the kidney. "Most" of the 80 C3H mice exposed to 400 ppm 1,2-dichloropropane died during the 37-exposure study, and only 3/80 C3H mice survived the exposures followed by a 7-month observation period; the 3 survivors had multiple hepatomas, but other histological effects were not noted.

It was reported in an abstract of a Soviet study that exposure to 9 mg/m^3 1,2-dichloropropane (~1.9 ppm) for 20 days elicited disruption of CNS function, blood enzyme activity, DNA synthesis (liver), and biological oxidation (liver, lungs and adrenals) in a group of 20 rats (Tsulaya et al., 1977). Additional details regarding the design and results of this study were not reported.

Chronic Toxicity. The only data regarding the non-neoplastic effects of chronic exposure to 1,2-dichloropropane are available from a National Toxicology Program carcinogenesis bioassay (NTP, 1986). As detailed in the Carcinogenicity Section, groups of 50 female F344/N rats and 50 B6C3F1 mice of each sex were gavaged with reagent grade 1,2-dichloropropane (~99.4% pure) in corn oil at doses of 0 (vehicle control), 125 or 250 mg/kg bw, 5 days/week for 103 weeks; groups of 50 male F344/N rats were similarly exposed to doses of 0, 62 or 125 mg/kg bw.

A dose-related depression in mean body weight was observed in dosed rats of both sexes throughout most of the study (NTP, 1986). The final body weights for the low-dose males, low-dose females, high-dose males and high-dose females were 5, 5, 14 and 24% less than control values, respectively. Survival was significantly ($p<0.001$) reduced in the high-dose female rats, but not in the low-dose female or male rats. In male rats 39/50 (78%) of the control, 42/50 (84%) of the low-dose, and 41/50 (82%) of the high-dose groups lived to the end of the study (105-108 weeks). In female rats 37/50 (74%) of the vehicle control, 43/50 (86%) of the low-dose, and 16/50 (32%) of the high-dose groups lived to the end of the study. The high-dose females had increased incidences of non-neoplastic liver lesions, although there was no increase in the incidence of liver tumors in the female rats (see Carcinogenicity Section); foci of clear cell change were found in 3/50 (6%) of the control, 5/50 (10%) of the low-dose and 11/50 (22%) of the high-dose groups. Necrosis (focal and centrilobular combined) occurred in 2/50 (4%) of the control, 1/50 (2%) of the low-dose and 12/50 (24%) of the high-dose groups of female rats. Mammary gland hyperplasia was increased in the low-dose but not high-dose female rats (controls, 10/50; low-dose,

20/50; high-dose, 1/50). This finding might possibly be due to the poor survival and an increased incidence of adenocarcinoma in the high-dose females (see Carcinogenicity Section). Treatment-related non-neoplastic effects were not observed in male rats.

Mean body weights of the treated and control mice were comparable throughout the course of the bioassay (NTP, 1986). Survival was reduced in the female mice [controls, 35/50 (70%); low-dose, 29/50 (58%); high-dose, 26/50 (52%)] after 105-107 weeks of exposure. The reduction in survival was statistically significant in the high-dose group. Infections of the reproductive tract, however, may have contributed to the decreased survival of the female mice; suppurative inflammation was found in the ovary, uterus or multiple organs of 5/11 control, 9/14 low-dose and 14/22 high-dose females that died before the end of the study. 1,2-Dichloropropane caused nonneoplastic liver lesions in male mice that included hepatomegaly (control, 3/50; low-dose, 5/49; high-dose, 15/50) and focal and centrilobular necrosis (control, 2/50; low-dose, 5/49; high-dose, 10/50). These lesions did not occur at increased incidences in treated female mice, but liver tumors were increased in both males and females (see Carcinogenicity Section). Acanthosis of the forestomach surface epithelium occurred at increased incidences in the high-dose males (control, 0/50; low-dose, 0/48; high-dose, 2/49) and low- and high-dose females (control, 0/50; low-dose, 5/50; high-dose, 4/50), a finding consistent with a slightly increased occurrence of forestomach squamous cell papillomas (see Carcinogenicity Section).

Target Organ Toxicity

The principal target organ for non-neoplastic effects of orally administered 1,2-dichloropropane in rats and mice is the liver (NTP, 1986). As detailed in the Subchronic Toxicity Section, hepatic lesions were found in male (centrilobular congestion) and female (centrilobular congestion, fatty changes and necrosis) F344/N rats that were gavaged with 1000 mg 1,2-dichloropropane/kg bw in corn oil, 5 days/week for 13 weeks. In the 2-year carcinogenesis bioassay (Carcinogenicity Section), treatment-related hepatic effects were found in female F344/N rats (foci of clear cell change, focal and centrilobular necrosis) and male $B6C3F_1$ mice (hepatomegaly, focal and centrilobular necrosis) that were exposed 5 days/week to 250 mg/kg bw. Similar hepatic effects were described in dogs 4 days following the administration of single oral doses of ~230-580 mg 1,2-dichloropropane/kg bw (Wright and Schaffer, 1932).

The liver also appears to be affected during acute and subchronic inhalation exposure to 1,2-dichloropropane (Highman and Heppel, 1946; Heppel et al., 1946, 1948; Sidorenko et al., 1976; Belyaeva et al., 1977). As detailed in the Acute Toxicity and Subchronic Toxicity Sections, laboratory rodents that died from several (<12) repeated daily 7-hour exposures of 1,2-dichloropropane at 1000-2200 ppm and mice that died or were killed after 14-28 4- to 7-hour exposures of 400 ppm exhibited liver histologic effects such as congestion, fatty degeneration and necrosis (Highman and Heppel, 1946; Heppel et al., 1946, 1948). Hepatic centrilobular necrosis was noted in rats treated for 2 days at 2200 ppm for 7 hours daily and became progressively more severe when treatment was extended (see Table V-2). Sidorenko et al. (1976) reported hepatic perilobular hyperplasia and hypertrophy,

reduction of centrilobular ribonuclear proteins, and reduced hepatic enzyme activity in rats treated at 216 or 432 ppm continuously for 7 days. Slight fatty degeneration of the liver was reported in C57 mice treated with 400 ppm 1,2-dichloropropane for 7 hours (Heppel et al., 1948). Similar liver histopathologic effects were noted in guinea pigs treated at 2200 ppm with a single 4- or 7-hour exposure or with 2, 3 or 4 daily 7-hour exposures. Corroboratively, Drew et al. (1978) reported significantly increased activities of SGOT, SGPT, and serum OCT in rats that were exposed to 1000 ppm 1,2-dichloropropane for a single 4-hour exposure.

Although the liver appears to be the primary target for 1,2-dichloropropane, the kidneys and adrenal gland are also important target organs. Gross observation of the kidneys of rats and mice exposed to 1,2-dichloropropane by gavage at doses of 2000 mg/kg bw/day and 500-1000 mg/kg/day, respectively, for 14 consecutive days showed the presence of red medullae (NTP, 1986). Histopathological effects in the kidney and adrenal medulla have also been described in rats and guinea pigs following inhalation exposure to 2200 ppm 1,2-dichloropropane for 4 or 7 hours (Highman and Heppel, 1946; Heppel et al., 1946); subchronic exposure to lower levels (1000 and 1500 ppm) also elicited adrenal effects (subcortical fibrosis) in guinea pigs (Heppel et al., 1946). Fatty degeneration of the kidney was observed in mice exposed by inhalation to 400 ppm 1,2-dichloropropane 4-7 hours/day, 5 days/week for 14-28 exposures (Heppel et al., 1948). Histological damage and suppression of oxidative enzymes were reported in the kidneys of rats treated with 216 or 432 ppm 1,2-dichloropropane continuously for 7 days (Sidorenko et al., 1976).

Other Effects

Carcinogenicity. An earlier draft of this document reviewed the NTP (1983) draft technical report. With the August publication of the final results (NTP, 1986) the incidence data changed slightly. In the carcinogenesis bioassay of 1,2-dichloropropane groups of 50 female F344/N rats, 50 male B6C3F1 mice and 50 female B6C3F1 mice were administered 1,2-dichloropropane in corn oil by gavage at doses of 0 (vehicle control), 125 or 250 mg/kg bw, 5 days/week for 103 weeks (calculated to 7 days/week these doses are 0, 89.3 or 178.6 mg/kg bw/day, respectively) (NTP, 1986). Groups of 50 male F344/N rats received doses of 0, 62 or 125 mg/kg bw on the same schedule (0, 44.3 or 89.3 mg/kg bw/day, respectively). The 1,2-dichloropropane was reagent grade with an approximate purity of 99.4% (toluene was identified as an impurity constituting 0.24% v/v of the product). The animals were 6-9 weeks of age at the start of the treatment. Necropsies with comprehensive histological examinations were performed on all animals found dead and on those killed at the end of the study, unless precluded by autolysis or cannibalization. As detailed in the Chronic Toxicity Section, survival was significantly reduced in the high-dose (250 mg/kg bw) female rats and female mice. Because of the reduced survival, statistical procedures adjusted for intercurrent mortality (life table and incidental tumor tests) were regarded as more meaningful than unadjusted analysis (Fischer exact test, Cochran-Armitage test for linear trend) (NTP, 1986). The design and results of the NTP (1986) bioassay of 1,2-dichloropropane are summarized in Table V-3.

Neoplastic lesions were not significantly increased in the treated male rats (NTP, 1986). Islet-cell carcinomas of the pancreas occurred with a

TABLE V-3

Summary of Gavage Carcinogenesis Bioassay of 1,2-Dichloropropane[a]

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (p value)[d]
Rat/ F344/N	M	125	5 days/week for 103 weeks	105-108 weeks	Pancreas (islet cell)	adenoma	3/50 (6%)
						carcinoma	3/50 (6%)
						adenoma or carcinoma	6/50 (12%)
		62	5 days/week for 103 weeks	105-108 weeks	Pancreas (islet cell)	adenoma	1/50 (2%)
						carcinoma	0/50 (0%)
						adenoma or carcinoma	1/50 (2%)
		0 (vehicle control)	5 days/week for 103 weeks	105-108 weeks	Pancreas (islet cell)	adenoma	4/48 (8%)
						carcinoma	0/48 (0%) (p=0.04)
						adenoma or carcinoma	4/48 (8%)
Rat/ F334/N	F	250	5 days/week for 103 weeks	105-108 weeks	Mammary gland	adenocarcinoma	5/50 (10%) (p=0.01N)[e]
						fibroadenoma	7/50 (14%) (p=0.045N)[f]
					Uterus	endometrial stromal polyp	11/50 (22%)
					Pituitary	adenoma	10/46 (22%) (p=0.17N)
						carcinoma	0/46 (0%)
						adenoma or carcinoma	10/46 (22%) (p=0.05N)

04/17/87

TABLE V-3 (cont.)

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Rat/ F344/N	F	125	5 days/week for 103 weeks	105-108 weeks	Mammary gland	adenocarcinoma	2/50 (4%)
						fibroadenoma	20/50 (40%)
					Uterus	endometrial stromal polyp	17/49 (35%)
					Pituitary	adenoma	26/50 (52%) (p=0.04)[f]
						carcinoma	2/50 (4%)
						adenoma or carcinoma	28/50 (56%)
		0 (vehicle control)	5 days/week for 103 weeks	105-108 weeks	Mammary Gland	adenocarcinoma	1/50 (2%)[e]
						fibroadenoma	15/50 (30%) (p=0.05N)[f]
					Uterus	endometrial stromal polyp	10/50 (20%)[g]
					Pituitary	adenoma	16/49 (33%)
						carcinoma	3/49 (6%)
						adenoma or carcinoma	19/49 (39%)
Mouse/ B6C3F1	M	250	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	17/50 (34%) (p=0.017)
						carcinoma	16/50 (32%)
						adenoma or carcinoma	32/50 (64%) (p=0.02)
		125	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	10/50 (20%)
						carcinoma	16/50 (34%)
						adenoma or carcinoma	26/50 (52%)

TABLE V-3 (cont.)

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Mouse/ B6C3F1	M	0	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	7/50 (14%) (p=0.01)
						carcinoma	11/50 (22%)
						adenoma or carcinoma	18/50 (36%) (p=0.002)
Mouse/ B6C3F1	F	250	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	5/50 (10%) (p=0.1)
						carcinoma	4/50 (8%)
						adenoma or carcinoma	9/50 (18%) (p=0.02)
					Thyroid follicular cell	adenoma	3/46 (7%)
						carcinoma	2/46 (4%)
						adenoma or carcinoma	5/46 (11%) (p=0.04)[e]
Mouse/ B6C3F1	F	125	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	5/50 (10%) (p=0.102)
						carcinoma	3/50 (6%)
						adenoma or carcinoma	8/50 (6%) (p=0.04)
					Thyroid follicular cell	adenoma	0/45 (0%)
						carcinoma	0/45 (0%)
						adenoma or carcinoma	0/45 (0%)

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Mouse/ B6C3F1	F	0 (vehicle control)	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	1/50 (0%) (p=0.09)
						carcinoma	1/50 (2%)
						adenoma or carcinoma	2/50 (2%) (p=0.02)
					Thyroid follicular cell	adenoma	1/48 (2%)
						carcinoma	0/48 (0%)
						adenoma or carcinoma	1/48 (2%) (p=0.03)

[a]Source: NTP, 1986

[b]50 animals/sex/dose tested

[c]Reagent grade 1,2-dichloropropane (~99.4% pure, containing 0.24% toluene) was administered in corn oil vehicle.

[d]The probability levels for the Fischer exact test for linear trend are given beneath the incidence of tumors in the dosed and control groups, respectively, when $p<0.05$. All values are nonsignificant unless other wise indicated.

[e]Significant ($p<0.05$) when adjusted for intercurrent mortality (life table and incidental tumor tests).

[f]Not significant ($p>0.05$) when adjusted for intercurrent mortality (life table and incidental tumor tests).

[g]Significant ($p<0.05$) when adjusted for intercurrent mortality (life table test).

01921
V 79
04/17/87

positive trend (significant Cochran-Armitage test) in male rats (see Table V-3), but this response was not considered to be treatment-related because the Fischer exact, life table and incidental tumor tests were not significant. In female rats, a significant dose-related increase in mammary gland adenocarcinomas (control, 1/50; low-dose, 2/50; high-dose, 5/50) was found after adjustment for intercurrent mortality. The majority of these tumors were found at the end of the study (control, 1/37; low-dose, 2/43; high-dose, 4/16), and it was noted that mammary gland adenocarcinomas are relatively uncommon in female F344/N rats (incidences in historical controls for the testing laboratory and for all NTP testing laboratories combined were 3/150 and 11/895, respectively). Mammary fibroadenomas were decreased in the high-dose female rats (control, 15/50; low-dose, 20/50; high-dose, 7/50). Endometrial stromal polyps occurred with a statistically significant positive trend (life table test), but the incidence was not significantly increased in the low- or high-dose groups. An increased incidence of pituitary adenomas in the low-dose females was statistically significant as determined by the Fischer exact test, but this increase was not significant when survival differences were taken into account (life table and incidental tumor tests) and the incidence of pituitary carcinomas was greater in the control than in the treated female rats. The high dose (250 mg/kg bw), however, was toxic for the female rats as reflected by reduced survival late in the study and lowered body weights (see Chronic Toxicity Section). The high-dose female rats also had increased incidences of non-neoplastic liver changes (see Chronic Toxicity Section), but there was no increase in the incidence of liver tumors.

Statistically significant dose-related increases of liver adenomas occurred in high-dose males (control, 7/50; low-dose, 10/50; high-dose, 17/50) and incidences were not statistically significant in females (control, 1/50; low-dose, 5/50; high-dose, 5/50) mice (see Table V-3) (NTP, 1986). The treated mice also had slightly higher incidences of liver carcinomas (male: control, 11/50; low-dose, 16/50; high-dose, 16/50; female: control, 1/50; low-dose, 3/50; high-dose, 4/50), but the increases were not statistically significant. As detailed in the Chronic Toxicity Section, non-neoplastic liver lesions were increased in male but not in female mice. The combined incidence of thyroid follicular cell adenomas or carcinomas was significantly elevated in the high-dose female mice after adjustment for intercurrent mortality and occurred with a significant positive trend, but no adenomas or carcinomas were observed in the low-dose female mice. 1,2-Dichloropropane was not, however, concluded to be a thyroid tumorigen in the female mice, apparently because the uncombined incidences of follicular cell adenomas and carcinomas were not significantly elevated. Squamous cell papillomas of the forestomach also occurred in the dosed male and female mice [males: control, 0/50 (0%); low-dose, 1/48 (2%); high-dose, 3/49 (6%), females: control, 0/50 (0%); low-dose, 2/50 (4%); high-dose, 2/50 (4%)]. The results of statistical analyses of these data were not reported, but it was noted that the historical incidences of squamous cell papillomas of the forestomach for the testing laboratory and for all NTP testing laboratories combined were 0/146 and 2/855 (0.2%), respectively, for males and 0/147 and 3/879 (0.3%), respectively, for females.

NTP (1986) concluded that the increased incidences of hepatocellular adenomas provided "some" evidence that 1,2-dichloropropane was carcinogenic

for both male and female B6C3F1 mice and that this evidence was strengthened by the slightly increased incidences of hepatocellular carcinomas in both sexes of mice. The increased incidence of mammary gland adenocarcinomas provided equivocal evidence of carcinogenicity in female F344/N rats because the increase was marginal and occurred only at the high dose level, which was toxic. No evidence of carcinogenicity for male F344/N rats was found.

In the only other study that reported neoplastic effects, 80 C3H mice were exposed by inhalation for 4-7 hours/day, 5 days/week to 400 ppm (1849 mg/m³) 1,2-dichloropropane (Heppel et al., 1948). After 37 exposures, the surviving mice ("most" died during the exposure period) were held for an observation period of 7 months. Only three mice survived to the end of the observation period with each exhibiting multiple hepatomas. The significance of these data is uncertain because of the high mortality. Additional detail regarding the design of this study is presented in the Subchronic Toxicity Section.

The direct bioassay data, according to a weight-of-evidence evaluation using EPA's Carcinogen Risk Assessment Guidelines, is equivalent to a Group C, but almost a Group B2 by virtue of the solid mouse response, together with some additional concern about the response seen in the female rat. There are no epidemiologic studies available on 1,2-dichloropropane.

Other considerations, including supporting data, are noteworthy. There is mutagenic activity evidence in short-term tests: Salmonella, forward mutation assays, in vitro sister-chromatid exchange and chromosome aberrations assays with hamster ovary cells. 1,2-Dichloropropane is metabolized

in the range of 20-35% in rats. The metabolites and pathways, some of which are hypothesized, include 1,2-epoxypropane and chloroacetaldehyde as intermediates. These intermediates are expected to have a carcinogenic potential. Also, 1,2-dichloropropane is structurally related to compounds with known carcinogenic activity in animal test systems including 1,2-dichloroethane, 1,2-dibromoethane and 1,2-dibromo-3-chloropropane.

These other considerations are strong enough to elevate the known high Group C evidence from the direct bioassays to a Group B2, meaning that there is sufficient evidence in animal test systems and that the compound should be considered a probable human carcinogen.

Mutagenicity. Mutagenicity and clastogenicity assays of 1,2-dichloropropane are summarized in Table V-4. In the reverse mutation assay with Salmonella typhimurium, 1,2-dichloropropane was mutagenic only in strains TA1535 and TA100. Both strains are sensitive to the production of mutations by base-pair substitutions. Negative results were obtained by NTP (1986) in plate incorporation assays at concentrations up to 2 mg/plate; however, De Lorenzo et al. (1977), Stolzenberg and Hine (1980), and Carere and Morpurgo (1981) reported positive results with concentrations of 10-50 mg/plate, both with and without activation by hepatic S9 mix. Positive results have also been obtained in spot tests (Carere and Morpurgo, 1981; Principe et al., 1981). Thus, at high concentrations, 1,2-dichloropropane appears to induce base-pair substitutions in S. typhimurium.

TABLE V 4

Mutagenicity/Clastogenicity of 1,2-Dichloropropane

Assay	Indicator/	Application	Concentration or Dose	Response +S9	Response -S9	Comment	Reference
Reverse mutation (histidine independence)	S. typhimurium TA100	plate incorporation	10, 20 or 50 mg/plate	-		NC	DeLorenzo et al., 1977
	TA1535			+	+		
				+	+		
Reverse mutation (histidine independence)	S. typhimurium TA100	plate incorporation	100 µmoles/plate	+	+	(+) at 100 µmoles/plate ±S9; (-) at 1 and 10 µmoles/plate ±S9	Stolzenberg and Hine, 1980
Reverse mutation (histidine independence)	S. typhimurium TA1535	plate incorporation	1, 2.5, 5 or 10 µl/plate			NC	Carere and Morpurgo, 1981
	TA100			+	+		
				+	+		
Reverse mutation (histidine independence)	S. typhimurium TA100	plate incorporation	0, 33, 100, 333, 1000 or 2000 µg/plate	-	-	"No clearly positive response was obtained." S9's from both rat and hamster livers were used	NTP, 1986
	TA98				-		
	TA1537			-	-		
	TA1535			-	-		
Reverse mutation (histidine independence)	S. typhimurium TA1535	spot test	0 or 10 µl/plate			NC	Principe et al., 1981
	TA100			+	+		
				+	+		
Reverse mutation (histidine independence)	S. typhimurium TA1535	spot test	0 or 10 µl/plate			1,2-Dichloropropane exerted a weak effect on the strains sensitive to mutation by base-pair substitution	Carere and Morpurgo, 1981
	TA1537			+	+		
	TA1538			-	-		
	TA98				-		
	TA100			-	-		
				+	+		
Foward mutation (streptomycin resistance)	Streptomyces coelicolor	plate incorporation	0, 2, 10, 20 or 100 µl/plate	NA	-	(-) at all concentrations tested	Principe et al., 1981
Forward mutation (streptomycin resistance)	Streptomyces coelicolor	plate incorporation	100-400 µl/plate	NA	-	NC	Carere and Morpurgo, 1981

TABLE V-4 (cont.)

Assay	Indicator/	Application	Concentration or Dose	Response +S9	Response -S9	Comment	Reference
Forward mutation (streptomycin resistance)	Streptomyces coelicolor	spot test	0 or 100 µl/plate	NA	-	NC	Principe et al., 1981
Forward mutation (8-azaguanine resistance)	Aspergillus nidulans	plate incorporation	0, 100, 200, 300 or 400 µl/plate	NA	+	NC	Principe et al., 1981
Foward mutation (8-azaguanine resistance, methionine suppression)	Aspergillus nidulans Strain 35 (pabaA1, anA1, yA2, meth61, nicA2, nic88)	plate incorporation	2-100 µl/plate	NA	+	NC	Carere and Morpurgo, 1981
Forward mutation (8-azaguanine resistance)	Aspergillus nidulans	spot test	0 or 300 µl/plate	NA	+	NC	Principe et al., 1981
Sister chromatid exchange	Chinese hamster ovary cells	liquid holding	112.7, 376.0 or 1127.0 µg/ml	+	+	NC	NTP, 1986
Chromosome aberration	Chinese hamster ovary cells	liquid holding	1180, 1370 or 1580 µg/ml (-S9); 460, 660 or 950 µg/ml (+S9)	+	+	NC	NTP, 1986

NA = Not applicable; NC = No comment

1,2-Dichloropropane was also shown to cause forward mutation to 8-azaguanine resistance and methionine supression in Aspergillus nidulans when tested with S9 activation (Carere and Morpurgo, 1981; Principe et al., 1981), but did not cause forward mutation to streptomycin resistance in Streptomyces coelicolor when tested without S9 activation (Carere and Morpurgo, 1981; Principe et al., 1981).

1,2-Dichloropropane induced sister chromatid exchanges and chromosome aberrations in Chinese hamster ovary cells that were exposed in vitro with and without S9 metabolic activation (NTP, 1986).

Teratogenicity and Other Reproductive Effects. Pertinent data regarding the teratogenic or reproductive effects of 1,2-dichloropropane were not located in the available literature.

Summary

Acute oral LD_{50}s of ~860, 2200, 2000 and 5000 mg 1,2-dichloropropane/kg bw have been reported for mice (Merck Index, 1976), rats (Smyth et al., 1969), guinea pigs (Farm Chemicals Handbook, 1980) and dogs (Wright and Schaffer, 1932), respectively. Daily administration of 1,2-dichloropropane to rats by gavage for 14 days produced 100% mortality and red renal medullae at a dose of 2000 mg/kg bw/day, and reduced body weight at 500-1000 mg/kg bw/day (NTP, 1986). Similar gavage administration to mice produced mortality and red renal medullae at doses as low as 500-1000 mg/kg bw/day (NTP, 1986). Treatment-related pathologic effects other than red renal medullae were not described in the rats or mice, but histological examinations were not conducted. In dogs, single oral doses of 1,2-dichloropropane in the

range of 230-580 mg/kg bw elicited signs of CNS depression and histological effects that occurred primarily in the liver (e.g., congestion, slight fatty degeneration), but also in the kidney and GI tract (Wright and Schaffer, 1932).

Inhalation exposure to ~2200 ppm 1,2-dichloropropane for 7 hours/day for 5-12 days (5 days/week) produced high mortality in rats, mice, guinea pigs and rabbits (Highman and Heppel, 1946; Heppel et al., 1948). With the exception of the mice, most animals of these species tolerated exposure to lower concentrations of 1,2-dichloropropane (1600-1000 ppm). Treatment-related histological effects typically included marked visceral congestion and fatty degeneration of the liver and kidney, and fibrotic changes were frequently described in the adrenals of guinea pigs. These effects were most frequent and extensive in the animals that died and in the animals exposed to the higher levels of 1,2-dichloropropane. Drew et al. (1978) found increased activities of serum enzymes that were indicative of liver damage in rats that were exposed for 4 hours to 1000 ppm 1,2-dichloropropane. In general, except for marked splenic hemosiderosis in rats and subcortical fibrosis of the adrenal in guinea pigs, animals that survived ~35 or more exposures (5 days/week) showed only occasional minimal histopathologic effects (Heppel et al., 1946). Significant treatment-related effects were not reported in rats and guinea pigs that received from 134-140 seven-hour inhalation exposures of 400 ppm 1,2-dichloropropane (5 days/week), but there was high mortality and fatty degeneration of the liver and kidneys in mice that received 14-28 similar 400 ppm exposures (Heppel et al., 1948).

Administration of 1,2-dichloropropane by gavage to rats at doses of 1000 and 500 mg/kg bw/day 5 days/week for 13 weeks produced 100% mortality (males and females) and 50% mortality (male rats), respectively, with histopathological effects in the liver (e.g., centrilobular congestion, necrosis and fatty changes). Mice that were administered 1,2-dichloropropane at levels of 250 or 500 mg/kg/day on the same dosing schedule exhibited no treatment-related weight depression, mortality or pathologic effects.

In a carcinogenesis bioassay 1,2-dichloropropane induced a statistically significant increased incidence of hepatocellular neoplasms (primarily adenomas in male and female B6C3F1 mice). The frequency of liver carcinomas alone were not statistically significant for either sex, but there was a numerical increase in both sexes. There was no statistically significant increase in tumors of any specific organ in F344 rats; however, there was a dose-related trend (by life table analysis) of mammary adenocarcinomas in the female rats. The increased adenocarcinoma incidence in the female rat is considered to be worthy of note since the F344 rat has a relatively low background increase of these tumors and NTP historical controls are less than the control values reported in this bioassay. Also, high mortality during the course of the bioassay may have precluded higher incidence observations. There is mutagenic activity evidenced in short-term tests: Salmonella, forward mutation assays, in vitro sister-chromatid exchange and chromosome aberration assays with hamster ovary cells. When 1,2-dichloropropane is metabolized, in the range of 20-35% in rats, the metabolites and pathways that are hypothesized include 1,2-epoxypropane and chloroacetaldehyde as intermediates, which can be expected to have a carcinogenic potential. Furthermore, 1,2-dichloropropane is structurally related to compounds

with known carcinogen activity in animal test systems including 1,2-dichloroethane, 1,2-dibromoethane and 1,2-dibromo-3-chloropropane.

When tested with and without metabolic activation, 1,2-dichloropropane has been reported to induce reverse mutation (histidine independence) in S. typhimurium (De Lorenzo et al., 1977; Stolzenberg and Hine, 1980; Carere and Morpurgo, 1981; Principe et al., 1981; NTP, 1986) and forward mutation (8-azaguanine resistance, methionine supression) in A. nidulans when tested with S9 activation (Carere and Morpurgo, 1981; Principe et al., 1981), but did not cause forward mutation (streptomycin resistance) in S. coelicolor when tested without activation (Carere and Morpurgo, 1981; Principe et al., 1981). Sister chromatid exchanges or chromosome aberrations were induced in Chinese hamster ovary cells that were exposed to 1,2-dichloropropane in vitro with and without metabolic activation (NTP, 1986).

Data regarding possible teratogenic or reproductive effects of 1,2-dichloropropane were not located in the available literature.

VI. HEALTH EFFECTS IN HUMANS

Pertinent data regarding the health effects of 1,2-dichloropropane in humans could not be located in the available literature; however, one abstract describing the effects of acute exposure of a 46-year-old man to an unspecified amount of 1,2-dichloropropane is reprinted below:

> Accidental ingestion of about 50 ml of a cleansing substance (containing 1,2-dichloropropane) in a 46-year-old man induced, within 2 hours, the appearance of a deep coma with hydriasis and hypertonia. Recovery of consciousness was obtained after 24 hours under artificial hyperventilation and osmotic diuresis. Then the patient suddenly developed an acute delirium with tremor and died at the 36th hour in a picture of irreversible shock with cardiac failure, lactic acidosis and hepatic cytolysis.
>
> Necrospy evidenced centro- and mediolobular acute hepatic necrosis. An analysis of the toxic substance by gas chromatography permited the identification of dichloropropane (Larcan et al., 1977).

Summary

One case study was located describing the effects of acute 1,2-dichloropropane exposure in a 46-year-old male. Larcan et al. (1977) reported that centro- and mediolobular hepatic necrosis was revealed at autopsy in a male who accidentally ingested an unspecified amount of 1,2-dichloropropane.

VII. MECHANISMS OF TOXICITY

Specific data regarding the mechanism of 1,2-dichloropropane toxicity could not be located in the available literature. Studies of the metabolism of 1,2-dichloropropane suggest that the major metabolic pathway involves the production of a reactive intermediate, the epoxide 1,2-epoxypropane (Jones and Gibson, 1980). 1,2-Epoxypropane is an alkylating agent, whereas 1,2-dichloropropane is not (Jones and Gibson, 1980). Some of the toxic effects of 1,2-dichloropropane may be due to this reaction intermediate, rather than to the parent compound. As reviewed by the NTP (1986), the centrilobular location of hepatic lesions resulting from 1,2-dichloropropane coincides with location of relatively high levels of microsomal enzymes, which activate short-chain, halogenated hydrocarbons to toxic intermediates.

1,2-Dichloropropane is known to have a number of biochemical and physiological effects as discussed previously (Chapter V, General Toxicity). Sidorenko et al. (1976) reported that the inhalation exposure of white rats to 1 or 2 mg/ℓ 1,2-dichloropropane caused suppression of enzyme activity and reduction in nucleoproteins in centrilobular sections of liver along with the suppression of oxidative enzymes and phosphomonoesterases in the kidney. Tsulaya et al. (1977) exposed rats to 9 mg/m³ 1,2-dichloropropane for 94 days and observed disruption of DNA synthesis in the liver and biological oxidation in the liver, lungs and adrenals.

Summary

Although the specific mechanism of 1,2-dichloropropane toxicity is not known, there is some evidence that the compound is metabolically activated to a toxic intermediate. 1,2-Dichloropropane has been reported to alter some biochemical parameters in the liver, kidneys, lungs and adrenals, but the toxicologic significance of these alterations is unclear.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = \text{____ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner,

the U.S. EPA (1986a) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD}) \times (\text{Body weight in kg})}{\text{Drinking Water Volume in } \ell\text{/day}} = ____ \text{ mg/}\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (___ \ell\text{/day})} = ____ \text{ mg/}\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these

estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is

uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Data for the toxicity of this compound to humans are limited to a single case of acute poisoning, reported only as an abstract (Larcan et al., 1977). Centro- and mediolobular hepatic necrosis were observed in a man who died 36 hours after ingesting ~50 mL of a cleansing substance. The toxic material was found to contain dichloropropane, but it is unclear whether it contained other compounds as well.

Single dose oral LD_{50}s of 2200 mg/kg bw for male rats (Smyth et al., 1969), 860 mg/kg bw for mice of unspecified sex (Merck Index, 1976), and 2000 mg/kg for guinea pigs of unspecified sex (Farm Chemicals Handbook, 1980) have been reported. Nonlethal effects of single oral doses have not been described in these species in the available literature, however, the single-dose LD_{50}s for the rats and mice are consistent with lethal dose levels reported in the NTP (1986) report in a 14-day gavage study.

In this 14-day study, groups of 5 male and 5 female F344 rats and 5 male and 5 female B6C3F1 mice were gavaged with 125, 250, 500, 1000 or 2000 mg/kg bw/day of 1,2-dichloropropane in corn oil (NTP, 1986). Observations included mortality, final body weights, and gross but not histologic observation of organs and tissues at necropsy. The only treatment-related effects of 1,2-dichloropropane in rats were 100% mortality and redness of the renal medullae (4/5 males, 5/5 females) at the 2000 mg/kg dose level, and reduced body weight in males and females receiving 1000 mg/kg and in males at 500 mg/kg. No effects were detected in rats administered 125 or 250 mg/kg. In mice, treatment-related effects were 100% mortality and red renal medullae in all 5 males and 5 females at 2000 mg/kg, and mortality (5/5 males and 4/5 females) and red renal medullae (0/5 males and 3/5 females) at 1000 mg/kg. No mortality occurred at lower dosages, but red renal medullae were seen in 3/5 males and 1/5 females at 500 mg/kg and in 0/5 males and 1/5 females at each of the remaining lower dosage levels. Body weights were not adversely affected.

Wright and Schaffer (1932) noted that a single oral dose of 5.1 mℓ/kg bw (~5.8 g/kg bw) but not 3.0 mℓ/kg bw (~3.5 g/kg bw) was fatal to individual dogs. In lower dose experiments, 11 dogs (strain and sex not specified) were given nonlethal single doses of 0.2 to 0.5 mℓ 1,2-dichloropropane/kg bw (~230-580 mg/kg bw) by stomach tube (Wright and Schaffer, 1932). Gross pathologic examinations of all of the dogs and histologic examinations of the liver and kidney from 5 of the 11 dogs were conducted 3-4 days following administration. Gross and microscopic changes in the liver (e.g., congestion, hemorrhage, slight cloudy swelling and fatty degeneration) were evident in all 11 dogs. Symptoms of

CNS depression (e.g., incoordination, loss of balance, unsteady gait, glazed eyes) were described in 5 of the 11 dogs. Renal effects (e.g., congestion, gross discoloration) and GI tract effects (e.g., hemorrhage and irritation) were evident in 4/11 and 6/11 dogs, respectively.

The acute inhalation toxicity of 1,2-dichloropropane has been investigated in rats, mice, guinea pigs, rabbits and dogs by Highman and Heppel (1946) and Heppel et al. (1946, 1948). Mice were more sensitive to inhaled 1,2-dichloropropane than were other species. Exposure to 400 ppm (1850 mg/m³) for 7 hours resulted in some deaths among C57 mice (Heppel et al., 1948). Mice that died or were killed after 1 or 2 such exposures had fatty degeneration of the liver and kidneys. No significant treatment-related effects were seen among other species exposed subchronically to 400 ppm (7 hours/day, 5 days/week), and virtually no histopathologic effects were seen in rats and guinea pigs killed after a few exposures (Heppel et al., 1948).

At 10,400 mg/m³ (~2200 ppm) for 7 hours, all exposed mice died; histopathologic examinations were not performed. Even at 4400 mg/m³ (~1000 ppm), all exposed mice died by 4 hours of exposure; histopathologic changes included fatty degeneration of the liver and kidneys (Heppel et al., 1946). Histopathologic effects were observed in the livers and kidneys of rats, guinea pigs and rabbits and in the adrenals of rats and guinea pigs following one or a few 7-hour exposures to 2200 ppm (~10,400 mg/m³) of 1,2-dichloropropane (Heppel et al., 1946; Highman and Heppel, 1946). A few deaths occurred among the rats and rabbits. A more recent acute inhalation study (Drew et al., 1978) in rats provided evidence of liver damage in rats exposed to 1000 ppm (~4630 mg/m³); SGOT, SGPT and OCT activities were increased.

The acute oral toxicity studies do not clearly define a NOEL or NOAEL for exposure to 1,2-dichloropropane. Mortality data from single-dose oral studies reported in the ~~draft~~ report (NTP, 1986) indicate that mice are more sensitive to 1,2-dichloropropane than are other species. In the report (NTP, 1986), an oral dose of 250 mg/kg bw/day had produced red renal medullae in 1 of 5 female mice in a 14-day study. The toxicological significance of this finding is unclear, as it was not investigated histologically.

The effect of 1,2-dichloropropane on the functional state of the liver in rats has been studied and reported in an abstract by Kurysheva and Ekshtat (1975). The groups of animals were given a daily dose of 14.4 mg/kg or 360 mg/kg of 1,2-dichloropropane orally for 30 days. The investigators reported that the levels of serum cholesterol, β-lipoprotein and γ-globulin increased after the 10th day following the daily administration of dosages. By the 20th day of dosing, the serum cholinesterase was inhibited, whereas the fructose-1-monophosphate aldolase, SGPT and SGOT enzyme activity was increased; after 30 days of dosing, SGPT was inhibited. Other information such as strain, number of animals, weight and age, as well as which doses caused which effects were not reported.

In another ingestion study in animals, Ekshtat et al. (1975) reported the results of orally administered 1,2-dichloropropane in rats. The animals were given a daily dose of 8.8, 44 or 220 mg/kg of 1,2-dichloropropane for 20 days. The investigators observed disturbances in the animals' protein formation, hepatic enzyme levels and lipid metabolism.

The only subchronic oral study available is the gavage study by the NTP (1986), in which 10 male and 10 female F344 rats were administered 0, 60, 125, 250, 500 or 1000 mg/kg bw/day and 10 male and 10 female B6C3F1 mice were administered 0, 30, 60, 125, 250 or 500 mg 1,2-dichloropropane/kg bw/day in corn oil by gavage (5 days/week) for 13 weeks. Observations included mortality, body weight, overt signs of toxicity and gross appearance of organs at necropsy. Animals in the 0, 500 and 1000 mg/kg groups were also examined histopathologically. In rats, the only treatment-related effects noted were mortality (20/20) with histopathologic effects in the livers of some but not all of the animals given 1000 mg/kg. Mortality also occurred in 5/10 male rats and 0/10 of the female rats with reduced mean terminal body weight in males in the 500 mg/kg group. In mice, 1 male from the 60 mg/kg group and 1 female from the 500 mg/kg group died. It is unclear whether these deaths were treatment-related and no other adverse effects were noted.

Only one chronic study has been performed. This study, NTP (1986), was designed primarily to investigate carcinogenic effects, but also provides some information on systemic toxicity. Groups of 50 female F344 rats and 50 male and 50 female B6C3F1 mice were administered 1,2-dichloropropane at 0, 125 or 250 mg/kg bw/day in corn oil by gavage (5 days/week) for ~2 years (103 weeks) (NTP, 1986). Groups of 50 male F344 rats were administered 1,2-dichloropropane at 0, 62 or 125 mg/kg bw/day in the same manner. Observations included survival, body weight, overt signs of toxicity, and gross and histological appearance of a wide range of organs and tissues. In rats, survival was decreased only among the females of the 250 mg/kg group.

An increased incidence of liver lesions (foci of clear cell change and focal and centrilobular necrosis) and decreased mean body weight were also observed in this group. At the 125 mg/kg dose level, survival among rats was unaffected, but males had decreased mean body weights and females had increased incidences of mammary gland hyperplasia. No adverse effects were observed in male rats given 62 mg/kg.

In mice, there was a decrease in survival among females receiving 125 and 250 mg/kg 1,2-dichloropropane. This decrease was statistically significant ($p<0.05$) at the higher dose. Survival of treated males was unaffected. The decreased survival of treated female mice was attributed, in part, to an increased incidence of severe infections of the reproductive tract for both low- and high-dose groups. The only other non-neoplastic effects in mice were increased incidences of liver lesions (hepatomegaly and focal and centrilobular necrosis) in males receiving 125 or 250 mg/kg.

Quantification of Noncarcinogenic Effects

The quantification of the critical effects of 1,2-dichloropropane requires consideration of the toxicity resulting from acute, subchronic and chronic exposure.

Derivation of 1-Day HA. There are insufficient toxicological data available in the published scientific literature to derive a 1-day HA. The data resulting from acute exposure to 1,2-dichloropropane from the NTP (1986) study in which 5 male and 5 female mice were administered by gavage 0, 125, 250, 500 or 1000 mg 1,2-dichloropropane/kg bw/day for 14 days came closest for 1-day HA consideration; however, the toxicological significance could not be assessed in absence of histological examination of tissues.

Derivation of 10-Day HA. Three studies in animals have been reported in the scientific literature in the form of an abstract or report (Kurysheva and Ekshtat, 1975; Ekshtat et al., 1975; NTP, 1986). However, these studies lack some relevant toxicological data necessary in the consideration of a 10-day HA. Kurysheva and Ekshtat (1975) reported the effect of 1,2-dichloropropane on the functional state of the liver of rats. The groups of animals were given a daily dose of 14.4 mg or 360 mg/kg of 1,2-dichloropropane orally for 30 days. The increase in the serum levels of serum cholesterol, lipoprotein, and gamma-globulin was noted after the 10th day following the daily administration of dosages. By the 20th day of dosing, the serum cholinesterase was inhibited, whereas the fructose-1-monophosphate aldolase, SGPT and SGOT enzyme activity was increased; after 30 days of dosing, SGPT was inhibited. Other information such as strain, number of animals, weight and age, as well as which doses caused what effects were not reported.

In another investigation study in animals, the Russian investigator Ekshtat et al. (1975) reported the results of orally administered 1,2-dichloropropane at dose levels of 8.8, 44 or 220 mg/kg for 20 days. The investigators observed disturbances in the animals' protein formation, hepatic enzyme levels and lipid metabolism. The NAS (1979), in a request from the U.S. EPA Office of Drinking Water, provided a 7-day level of 1,2-dichloropropane based on Ekshtat et al. (1975) study in rats. The following formula was used to derive a 7-day level for a 70 kg man consuming 2 ℓ water/day.

$$\frac{8.8 \text{ mg/kg/day} \times 70 \text{ kg}}{1000 \times 2 \text{ ℓ}} = 0.3 \text{ mg/ℓ for a 70 kg adult}$$

where:

8.8 mg/kg/day = minimal effect level from the subacute ingestion studies in rats

70 kg = average weight of an adult

1000 = uncertainty factor because the data are limited and incomplete

2 ℓ = water consumption/day

In the case of a 10 kg child, the level of 1,2-dichloropropane would be:

$$\frac{8.8 \text{ mg/kg/day} \times 10 \text{ kg}}{1000 \times 1 \text{ ℓ}} = 0.088 = 0.09 \text{ mg/ℓ for a 10 kg child}$$

If the NAS (1979) recommended level of 0.3 for a 70 kg adult is acceptable for a 7-day exposure of 1,2-dichloropropane, this guidance could also be considered for a 10-day HA.

In the NTP (1986) study, 10 male and 10 female F344 rats were administered 0, 60, 125, 250, 500 or 1000 mg/kg bw/day and 10 male and 10 female B6C3F1 mice were given 0, 30, 60, 125, 250, 500 mg/kg bw/day of 1,2-dichloropropane in corn oil gavage for 13 weeks. Observations included mortality, body weight, overt signs of toxicity and gross appearance of organs at necropsy. Animals in the 0, 500 and 1000 mg/kg groups were examined histopathologically. In rats, the treatment-related effects were mortality of all 20 rats and histopathologic effects in the livers of some of the animals at 1000 mg/kg, and mortality in males (5/10) and females (0/10) and reduced mean terminal body weight in males at 500 mg/kg. In mice, 1 male from the 60 mg/kg group and 1 female from the 500 mg/kg group died. It is unclear whether these deaths were treatment-related.

In view of the inadequacy of toxicological data specified in the above studies, it is prudent not to derive a 10-day HA at this time.

Derivation of Longer-Term HA. Data are inadequate to develop a longer-term HA for 1,2-dichloropropane.

Assessment of Lifetime Exposure and Derivation of a DWEL. Only one chronic ingestion study has been carried out. This study (NTP, 1986) was designed primarily to investigate carcinogenic effects; it also provides data on nontumor pathology. In this study groups of 50 F344 rats were administered 1,2-dichloropropane at 0, 125 or 250 mg/kg (females) or 0.62 or 125 mg/kg (males) in corn oil by gavage (5 days/week) for ~2 years (103 weeks). Observations included survival, body weight, overt signs of toxicity, and gross and histological appearance of a wide range of organs and tissues. Survival was decreased only among the females of the 250 mg/kg group. An increased incidence of liver lesions (foci of clear cell change and focal and centrilobular necrosis) and decreased mean body weight were also observed in this group. At the 125 mg/kg dose level, males had decreased mean body weights and females had increased incidences of mammary gland hyperplasia. No adverse effects were observed in male rats given 62 mg/kg. The 62 mg/kg (TWA=44.3 mg/kg bw/day) dose is therefore identified in this study as a NOAEL.

The NTP (1986) study was considered for use in deriving the lifetime DWEL. However, because the resulting concentration in drinking water would be a couple of orders of magnitude higher than the concentration associated with a cancer risk level of 10^{-4}, it is not recommended that a DWEL be calculated.

Carcinogenic Effects

1,2-Dichloropropane induces a statistically significant increased incidence of hepatocellular neoplasms, primarily adenomas in male and female B6C3f1 mice. The frequency of liver carcinomas alone were not significant for males or females but there was a numerical increase in both sexes. There was no statistically significant increase in tumors of any specific organ in F344 rats; however, there was a dose-related trend (by life table analysis) on mammary adenocarcinomas in the female rats. The increased adenocarcinoma incidence in the female rat is considered to be worthy of note since the F344 rat has a relatively low background increase for these tumors and NTP historical controls are less than the control values reported in this bioassay. Also high mortality during the course of the bioassay may have precluded higher incidence observations.

The direct bioassay data, according to a weight-of-evidence evaluation using EPA's Carcinogen Risk Assessment Guidelines, is equivalent to a Group C, almost a Group B2 by virtue of the solid mouse response together with some additional concern about the response seen in the female rat. There are no epidemiologic studies available on 1,2-dichloropropane. Other considerations, i.e., supporting data, are noteworthy. There is mutagenic activity evidenced in short-term tests: Salmonella, forward mutation assays, in vitro sister-chromatid exchange and chromosome aberration assays with hamster ovary cells. 1,2-Dichloropropane is metabolized in the range of 20-35% in rats. The metabolites and pathways, some of which are hypothesized, include 1,2-epoxypropane and chloroacetaldehyde as intermediates. These intermediates are expected to have a carcinogenic potential. 1,2-Dichloropropane is structurally related to compounds with known carcinogenic activity in animal test systems including 1,2-dichloroethane, 1,2-dibromo-

ethane and 1,2-dibromo-3-chloropropane. The other considerations are strong enough to elevate the Group C evidence from the direct bioassays to a Group B2 means that there is sufficient evidence in animal test systems and that the compound should be considered a probable human carcinogen.

Quantification of Carcinogenic Effects

The dose-response data for hepatocellular adenoma and carcinoma in B6C3F1 mice (NTP, 1986), shown in Table VIII-1, can be used for quantitative assessment of cancer risk from exposure to 1,2-dichloropropane. Based on these data and using a linearized multistage model adopted by the U.S. EPA (45 FR 79318), a carcinogenic potency factor (q_1^*) for humans of 6.7×10^{-2} $(mg/kg/day)^{-1}$ was calculated from the data for male mice and a q_1^* of 2.2×10^{-2} $(mg/kg/day)^{-1}$ was calculated from the data for female mice. The higher of the two values is the appropriate basis for the estimation of cancer risk levels. The upper-limit unit risk estimates from the

animal data are derived from a linearized multistage nonthreshold extrapolation model which is currently programmed as GLOBAL 83. Justification for its use is presented in EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986b). While recognizing that alternative statistical modeling approaches exist [e.g., One-hit, Weibull, Log-Probit and Logit models, and maximum likelihood estimates], the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of approach consistency and of providing an upper bound estimate for the potential cancer risk, the Agency recommends the use of the linearized multistage model. EPA consider this model and resulting risk estimate to be an upper limit value in the sense that the true risk is unlikely to be higher and may be lower even zero. An established procedure does not yet exist for making "most likely" or "best" estimates of risk within the range of uncertainty derived by the upper and lower limit values.

The doses corresponding to increased lifetime cancer risks for a 70 kg man of 10^{-4}, 10^{-5} and 10^{-6} are 1.04×10^{-1}, 1.04×10^{-2} and 1.04×10^{-3} mg/day, respectively. Assuming a water consumption of 2 ℓ/day, the corresponding concentrations of 1,2-dichloropropane in water are $\sim 5.2 \times 10^{-2}$, 5.2×10^{-3} and 5.2×10^{-4} mg/ℓ, respectively. Other cancer-based criteria could not be located in the available literature.

Existing Guidelines and Standards

The ACGIH (1983) has adopted a TLV of 75 ppm (~350 mg/m³) and STEL of 110 ppm (~500 mg/m³) for 1,2-dichloropropane in workroom air. The TLV represents a TWA concentration for an 8-hour day or 40-hour workweek. The TLV and STEL are based primarily on the data of Heppel et al. (1946, 1948).

The Occupational Safety and Health Administration (OSHA) standard for 1,2-dichloropropane in workplace air is also 75 ppm as an 8-hour TWA (29 CFR 1910).

The U.S. EPA (1980a) concluded that data regarding the toxicity of 1,2-dichloropropane were insufficient for the derivation of an ambient water quality criterion for the protection of human health.

Special Considerations

Synergistic Effects. Drew et al. (1978) studied the effects of 1,2-dichloropropane in combination with trichloropropane on rat serum enzymes. Male CD-1 rats were exposed by inhalation to a mixture of 1000 ppm (4621.7 mg/m^3) 1,2-dichloropropane and 500 ppm (2310.8 mg/m^3) trichloropropane for 4 hours. Levels of SGOT, SGPT, glucose-6-phosphatase and OCT were measured 24 and 48 hours after a single exposure to the mixture. An initial depression in the level of glucose-6-phosphatase was observed on the day of exposure and within the first 24 hours. SGOT, SGPT and OCT were all increased after exposure to the mixture. According to the authors, the compounds had an additive effect for SGOT and OCT at 24 hours. The only greater-than-additive (synergistic) effect was observed for SGPT at 24 hours; however, this effect decreased by 48 hours and was significantly less-than-additive (antagonistic) for SGOT, SGPT and OCT by 48 hours. Thus, results of this study suggested that 1,2-dichloropropane and trichloropropane did not act in a synergistic manner with respect to the levels of serum enzymes in the rat.

High Risk Subpopulations. Human data that would establish the existence of sensitive subpopulations were not found in the literature searched. Data from animal studies suggest considerable inter- and intraspecies differences in susceptibility (see the Noncarcinogenic Effects Section). In addition, individuals who are exposed occupationally to 1,2-dichloropropane (e.g., agricultural workers and those involved in the manufacture of the chemical) may be at somewhat greater risk because of their additional exposure.

Summary

The data base for the toxicity of 1,2-dichloropropane is limited, consisting of a number of studies from the older literature and the NTP (1986) report of toxicology and carcinogenesis studies.

No drinking water criteria have been recommended due to the inadequacy of available toxicological studies. In the case of the lifetime DWEL, a 2-year gavage study in rats (NTP, 1986) is not recommended because of the carcinogenic potency of 1, 2-dichloropropane.

Based on the heptatocellular adenoma and carcinoma response of male mice given 1,2-dichloropropane by gavage (NTP, 1986), an excess lifetime cancer risk at 10^{-4}, 10^{-5} and 10^{-6} associated with water concentration would be 5.2×10^{-2}, 5.2×10^{-3} or 5.2×10^{-4} mg/l, respectively. This information is summarized in Table VIII-2.

TABLE VIII-2

Criteria for 1,2-Dichloropropane

Criteria	mg/L	mg/kg bw/day
1-day HA (child)	insufficient data	--
10-day HA (child)	insufficient data	--
Longer-term HA (child/adult)	insufficient data	--
Lifetime DWEL	not calculated*	--
10^{-4} Excess Cancer Risk	5.2×10^{-2}	1.5×10^{-3}
10^{-5} Excess Cancer Risk	5.2×10^{-3}	1.5×10^{-4}
10^{-6} Excess Cancer Risk	5.2×10^{-4}	1.5×10^{-5}

*The DWEL was not calculated because the resulting concentration in drinking water would be a couple of orders of magnitude higher than the concentration associated with a cancer risk level of 10^{-4}.

IX. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983-1984. Cincinnati, OH. p. 30.

BCPC (British Crop Protection Agency). 1977. Pesticide Manual Basic Information on the Chemicals used as Active Components of Pesticides, 5th ed., H. Martin and C.R. Worthing, Ed. p. 178.

Belyaeva, N., B. Bonashevskaya, T. Marshak and V. Brodskii. 1977. Investigation of the effect of certain chlorinated hydrocarbons on the composition of hepatocytes population of the rat liver. Bull. Exp. Biol. 83: 396-400.

Bonashevskaya, T.I., V.R. Tsulaya, V.V. Zykova, N.B. Kumpan and V.V. Shaipak. 1978. Effect of chlorine derivatives of propane and ethylene on white rat lungs. Subacute experiment. Deposited Doc. No. VINITI 17331778. p. 11. CA 91:187533.

Burns, L.H., D.M. Cline and R.R. Lassiter. 1981. Exposure analysis modeling system (EXAMS). Prepared by Environmental Research Lab, ORD, U.S. EPA, Athens, GA.

Callahan, M.A., M.W Slimak, N.W. Gabel et al. 1979. Water-related environmental fate of 129 priority pollutants, Vol. II, Off. Water Plan. Stand., Off. Water Wastewater Manage., U.S. EPA, Washington, D.C. EPA-440/4-70-029b.

Carere, A. and G. Morpurgo. 1981. Comparison of the mutagenic activity of pesticides *in vitro* in various short-term assays. Prog. Mutat. Res. 2: 87-104.

Chiou, C.T., V.H. Freed, L.J. Peters and R.L. Kohnept. 1980. Evaporation of solutes from water. Environ. Int. 3: 231-236.

DeLorenzo, F., S. Degl'Innocenti, A. Ruocco, L. Silengo and R. Cortese. 1977. Mutagenicity of pesticides containing 1,3-dichloropropane. Cancer Res. 37: 1915-1917.

Dewalle, F.B. and E.S.K. Chian. 1978. Presence of trace organics in the Delaware River and their discharge by municipal and industrial sources. Proc. Ind. Waste Conf. 32: 908-19.

Dreisch, F.A., M. Gower and T.O. Munson. 1980. Survey of the Huntington and Philadelphia River Water Supplies for Purgeable Organic Contaminants. U.S. EPA, Annapolis, MD. EPA 903/9-81-003. 14 p.

Drew, R.T., J.M. Patel and F.N. Lin. 1978. Changes in serum enzymes in rats after inhalation of organic solvents singly and in combination. Toxicol. Appl. Pharmacol. 4593: 809-819.

Ekshtat, B., N.G. Kurysheva, V.N. Fedyana and M.N. Pavelenko. 1975. Study of the cumulative properties of substances at different levels of activity. Uch. Zap. Mosk. Nauchno-Issled. Inst. Zig. 22: 46-48.

Farm Chemicals Handbook. 1980. 1,2-Dichloropropane. Meister Publishing, Willoughby, OH. p. 256. (Cited in NIOSH, 1983)

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons, NY. 339 p.

Hawley, G.G. 1977. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Co., NY. p. 864.

Heppel, L.A., P.A. Neal, B. Highman and V.T. Potterfield. 1946. Toxicology of 1,2-dichloropropane. I. Studies on effects of daily inhalations. J. Ind. Hyg. Toxicol. 28: 1-8.

Heppel, L.A., B. Highman and E.Y. Peake. 1948. Toxicology of 1,2-dichloropropane. IV. Effects of repeated exposures to a low concentration of the vapor. J. Ind. Hyg. Toxicol. 30: 189-191.

Highman, B. and L.A. Heppel. 1946. Toxicology of 1,2-dichloropropane (propylene dichloride). III. Pathologic changes produced by a short series of daily exposures. Arch. Path. 42: 525-534.

Hutson, D.H., J.A. Moss and B.A. Pickering. 1971. Excretion and retention of components of the soil fumigant D-D and their metabolites in the rat. Food Cosmet. Toxicol. 9(5): 677-680.

Jones, A.R. and J. Gibson. 1980. 1,2-Dichloropropane: Metabolism and fate in the rat. Xenobiotica. 10(11): 835-846.

Kawasaki, M. 1980. Experiences with the test scheme under the chemical control law of Japan. An approach to structure-activity correlation. Ecotoxic. Environ. Safety. 4: 444-454.

Kurysheva, N.G. and B.Y. Ekshtat. 1975. Effect of 1,3-dichloropropylene and 1,2-dichloropropane on the functional state of the liver in animal experiments. Uch. Zap.-Mosk. Nauchno-Issled. Inst. Gig. 22: 89-92. (CA 86:115725)

Larcan, A., H. Lambert, M.C. Kaprevok and B. Gustin. 1977. Acute poisoning induced by dichloropropane. Acta. Pharmacol. Toxicol. 41: 330. (Abstr.)

Mabey, W.R., J.H. Smith, R.T. Podoll et al. 1981. Aquatic fate process data for organic priority pollutants. U.S. EPA, Washington, DC. EPA 440/4-81-014.

Merck Index. 1976. Merck Index: An Encyclopedia of Chemicals and Drugs, 8th and 9th ed. Merck and Co., Rahway, NJ. 9: 1017. (Cited in NIOSH, 1983)

NAS (National Academy of Sciences). 1977. Drinking Water and Health. Vol. 1, p. 19-63.

NAS (National Academy of Sciences). 1980. Drinking Water and Health. Vol. 3, p. 25-67.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS (Registry of Toxic Effects of Chemical Substances). October, 1983: Online.

NTP (National Toxicology Program). 1986. NTP technical report no. 263 on the toxicology and carcinogenicity studies of 1,2-dichloropropane (CAS No. 78-87-5) in F344/N rats and B6C3F$_1$ mice (gavage study). June. NIH Publ. No. 83-2519. August, 1986.

Ohio River Valley Water Sanit. Comm. 1979. Water treatment process modifications for trihalomethane control and organic substances in the Ohio River. Prepared for Project Activities 10/76-8/79, Cincinnati, OH.

Ohio River Valley Water Sanit. Comm. 1980. Assessment of water quality conditions. Ohio River Mainstem 1978-79, Cincinnati, OH.

Principe, P., E. Dogliotti, M. Bignami et al. 1981. Mutagenicity of chemicals of industrial and agricultural relevance in Salmonella, Streptomyces and Aspergillus. J. Sci. Food Agric. 32(8): 826-832.

Sax, N.I. 1975. Dangerous Properties of Industrial Materials. Reinhold Book Corp., NY. p. 1064.

Sidorenko, G.I., V.R. Tsulaya, E.I. Korenevskaya and T.I. Bonashevskaya. 1976. Methodological approaches to the study of the combined effect of atmospheric pollutants as illustrated by chlorinated hydrocarbons. Environ. Health. Perspect. 13: 111-116.

Smyth, H.F., Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J.A. Striegel and J.S. Nycum. 1969. Range-finding toxicity data, VII. Am. Ind. Hyg. Assoc. J. 30(5): 470-476.

Stolzenberg, S.J. and C.H. Hine. 1980. Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. Environ. Mutagen. 2(1): 59-66.

Tabak, H.H., S.A. Quave, C.I. Mashni and E.F. Barth. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53: 1503-1518.

Torkelson, T.R. and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons. In: Toxicology, Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B, G.D. Clayton and E.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 3529-3532.

Tsulaya, V.R., T.I. Bonashevskaya, V.V. Zykova et al. 1977. Toxicological features of certain chlorine derivatives of hydrocarbons. Gig. Sanit. 8: 50-53. (CA 87:128362)

U.S. EPA. 1980a. Ambient Water Quality Criteria for Dichloropropanes/propenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-043. NTIS PB81-117541.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 49347-49357.

U.S. EPA. 1986a. Appendix A. Reference Dose (RfD): Description and Use in Health Risk Assessment. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

Van Dyke, R.A. and C.G. Wineman. 1971. Enzymatic dechlorination of chloroethanes and propanes in vitro. Biochem. Pharmacol. 20: 463-470.

Wright, W.H. and Schaffer, J.M. 1932. Critical antihelminthic tests of chlorinated alkyl hydrocarbons and a correlation between the antihelminthic chemical structure and physical properties. Am. J. Hyg. 16: 325-428.